CONTENTS

The American Journal of Medicine

VOL. VI FEBRUARY, 1949 No. 2

Editorial

Clinical Studies

Review

Contents continued on page 5

liver disorders

cirrhosis
fat infiltration
functional impairment
toxic hepatitis
infectious hepatitis

methischol

(pronounced meth' is kol)

A synergistic combination of METHIONINE, CHOLINE and INOSITOL in a LIVER-VITAMIN B COMPLEX BASE . . . lipotropic substances which favor the transport of fat from the liver to the fat depots of the body . . . for prophylaxis, retardation and specific therapy in reparable liver damage.

each tablespoonful or 3 capsules contain:

dl-Methionine ..... 333 mg.
Choline ..... 250 mg.
Inositol ..... 166 mg.
together with the natural B complex from 12 grams of liver.

Supplied, in bottles of 100, 250, 500 and 1000 capsules and 16 oz. and gallon syrup.

advantages of **methischol**

1. three efficient lipotropic agents.
2. natural B complex from liver.
3. essential, readily utilized METHIONINE.
4. well tolerated, non-toxic, convenient.

Detailed literature and sample.

u. s. vitamin corporation
casimir funk labs., inc. (affiliate)
250 east 43rd street • new york 17, n. y.

CONTENTS

The American Journal of Medicine

VOL. VI FEBRUARY, 1949 NO. 2

Contents continued from page 3

Seminars on Mechanisms of Congestive Failure

Conference on Therapy

Clinico-pathologic Conference

Case Reports

General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

Articles are accepted for publication with the understanding that they are original contributions never previously published. All manuscripts are subject to editorial modification, and upon acceptance become the property of THE AMERICAN JOURNAL OF MEDICINE.

THE AMERICAN JOURNAL OF MEDICINE does not hold itself responsible for any statement made or opinions expressed by any contributor in any article published in its columns.

A reasonable number of illustrations are supplied free of cost; special arrangements must be made with the editor and publishers for excess illustrations and elaborate tables.

Reprints are furnished on order. Prices are quoted on the first day of the month during which article appears. Individual reprints of an article must be obtained from the author.

Change of address must reach us by the 15th of the month preceding month of issue.

PREPARATION OF MANUSCRIPTS

Text. Manuscripts are to be typewritten on one side of the paper, with double spacing and good margins. The original should be sent to the editor and a carbon copy retained by the author.

Illustrations. Illustrations must be in the form of glossy prints or drawings in black ink (*never* in blue). On the back of each illustration the figure number, author's name and an indication of the top of the picture should be given. Legends for illustrations are to be typewritten in a single list, with numbers corresponding to those on the photographs and drawings. Please do not attach legends to the pictures themselves.

Bibliographies. Bibliographic references should be at the end of the manuscript and not in footnotes. Each reference should include the following information in the order indicated: Name of author with initials; title of article; name of periodical; volume, page and year. The following may be used as a model:

BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am J. Surg.*, 26: 648, 1945.

The subscription price of THE AMERICAN JOURNAL OF MEDICINE, is $10.00 per year in advance in the United States; $12.00 in Canada and Pan-American countries and $15.00 in foreign countries. Current single numbers $2.00. All Special Numbers $4.00. Prices for such back numbers as are available will be quoted on request.

Address all correspondence to

The American Journal of Medicine · 49 West 45th Street · New York 19

Case History of an overweight streetcar-operator . . .

'Dexedrine' Sulfate—because it curbed appetite and lowered food intake—enabled even this extremely obese patient to lose weight easily and safely without the use (and risk) of such potentially dangerous drugs as thyroid.

Patient before treatment (age 53; height 5' 10½") weighed 352 pounds . . . was suffering from hypertension, nervousness and dyspnea . . . lived in fear of causing an accident while on duty. Overeating was the only demonstrable cause of his obesity.

Therapy: 'Dexedrine' (15 mg. A.C.t.i.d.)	Results: Weight	B. P.	Pulse
March, 1946 . . . . . 'Dexedrine' therapy begun	352	280/152	86
November, 1946 . . 8th month of 'Dexedrine' therapy .	269	160/84	86
January, 1948 . . . . 22nd month of 'Dexedrine' therapy .	234	158/84	86

In addition to the weight reduction of 118 pounds and the concurrent lowering of blood pressure, a remarkable improvement is reported in the patient's mood and outlook. Earlier nervousness and fears have vanished.

Dexedrine* Sulfate tablets and elixir . . . . the most effective drug for control of appetite in weight reduction.

Smith, Kline & French Laboratories Philadelphia

*T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

To forestall this eventuality

Syrup CHOLINE BICARBONATE

When instituted early and in conjunction with a diet providing large amounts of protein and B complex vitamins, Choline therapy interrupts the chain of events in the development of portal cirrhosis. Thus fatty infiltration of the liver, the forerunner of cirrhosis, is overcome, and the fatal complicating cirrhosis is either forestalled or prevented.

Syrup Choline Bicarbonate-C.S.C., an entirely new choline preparation for therapeutic use, is an advantageous means of administering choline. It is an unusually palatable mixture, provides the equivalent of 12.5 per cent choline base or 14.4 per cent choline chloride, and may be given in full therapeutic dosage without gastric intolerance or nausea.

Available at all pharmacies in one pint bottles.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION • 17 EAST 42nd STREET • NEW YORK 17, N. Y.

Transports hydrochloric acid and pepsin from the stomach.

Releases these agents in the proper environment for inactivation of pepsin and harmless neutralization of hydrochloric acid.

Effects prompt symptomatic relief.

Healing of the ulcer crater occurs "much more rapidly...than...with aluminum preparations."[1]

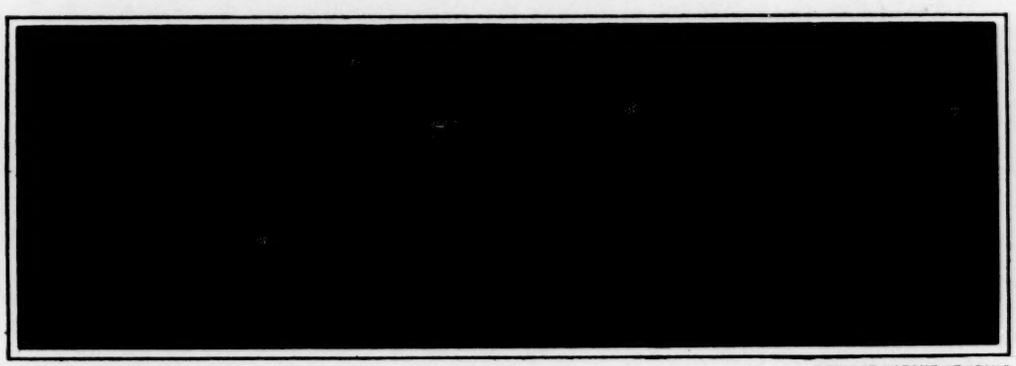
ACTION WITHOUT REACTION

Completely nontoxic anion exchange resin; chemically inert, insoluble and nonirritating.

Cannot produce alkalosis or acid rebound.

Does not remove chloride or phosphate ions.

Unlike magnesium or aluminum preparations, has no effect on the bowel.



RESINAT PATENT PENDING

Supplied:
Resinat Capsules (0.25 Gm.)
50's, 100's, 500's and 1,000's.

Resinat Powder (1 Gm. packets)
50's and 100's.

Dosage: 0.5 Gm. to 1 Gm. every 2 hours while awake. Following x-ray regression of the ulcer crater (usually 10-14 days)[1] dosage may be gradually reduced to a maintenance level; 0.5 Gm. 1 hour after meals and at bedtime.

1. Weiss, J.: Review of Gastroent., 15:826, Nov., 1948.

THE NATIONAL DRUG COMPANY, PHILADELPHIA 44, PA.

Manufacturers of

Pharmaceutical, Biological and Biochemical Products for the Medical Profession

FOR AS LONG AS 14 HOURS

IN HY[illegible]

One of the [illegible]

Vertavis®

VERTAVIS is the only drug, of all the hypotensive agents tested, which meets this criterium—in fact, the duration of action of VERTAVIS is *as long as 14 hours.* According to clinical investigations, the hypotensive effect of VERTAVIS "usually begins in one or two hours, reaches a maximum in four to six hours, and ends in ten to fourteen hours."[1,2,3]

Successful therapy with VERTAVIS, therefore, depends upon time-dose relationship. For full information on clinical findings, indications and administration, write for free illustrated brochure on VERTAVIS.

VERTAVIS in tablet form contains veratrum viride as the whole-powdered drug, selected and collected under rigid controls, and biologically assayed in CRAW UNITS—an Irwin-Neisler research development.

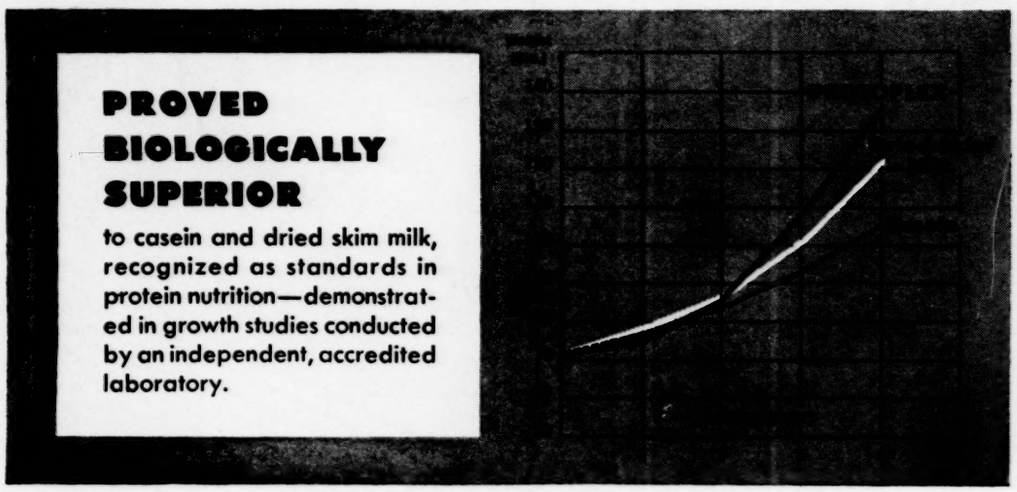
Supplied: Vertavis 10 Craw Units
Vertavis with Phenobarbital
Vertavis 5 Craw Units
In bottles of 100, 500, 1000.

1. Freis, E. D.: Med. Clin. N. Am. 32: 1247-1258, 1948.
2. Freis, E. D., and Stanton, J. R.: Am. Heart J. 36: 723-738, 1948.
3. Barker, H., et al: Paper Presented before Am. Coll. Phys., Chicago, May, 1947.

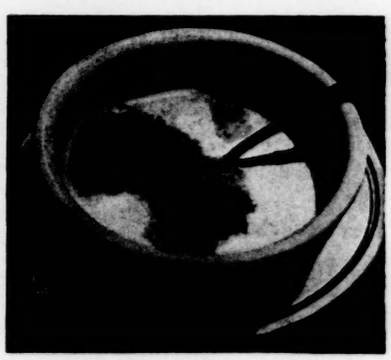
IRWIN, NEISLER & CO. 63 YEAR Irwin **DECATUR, ILLINOIS**

PROTOPLEX

Whole Mixed Protein plus Whole Liver and Yeast



PROTOPLEX* provides all the essential and nonessential amino acids as present in casein, lactalbumin, primary dried yeast U.S.P., and desiccated whole liver. Relatively salt- and fat-free.



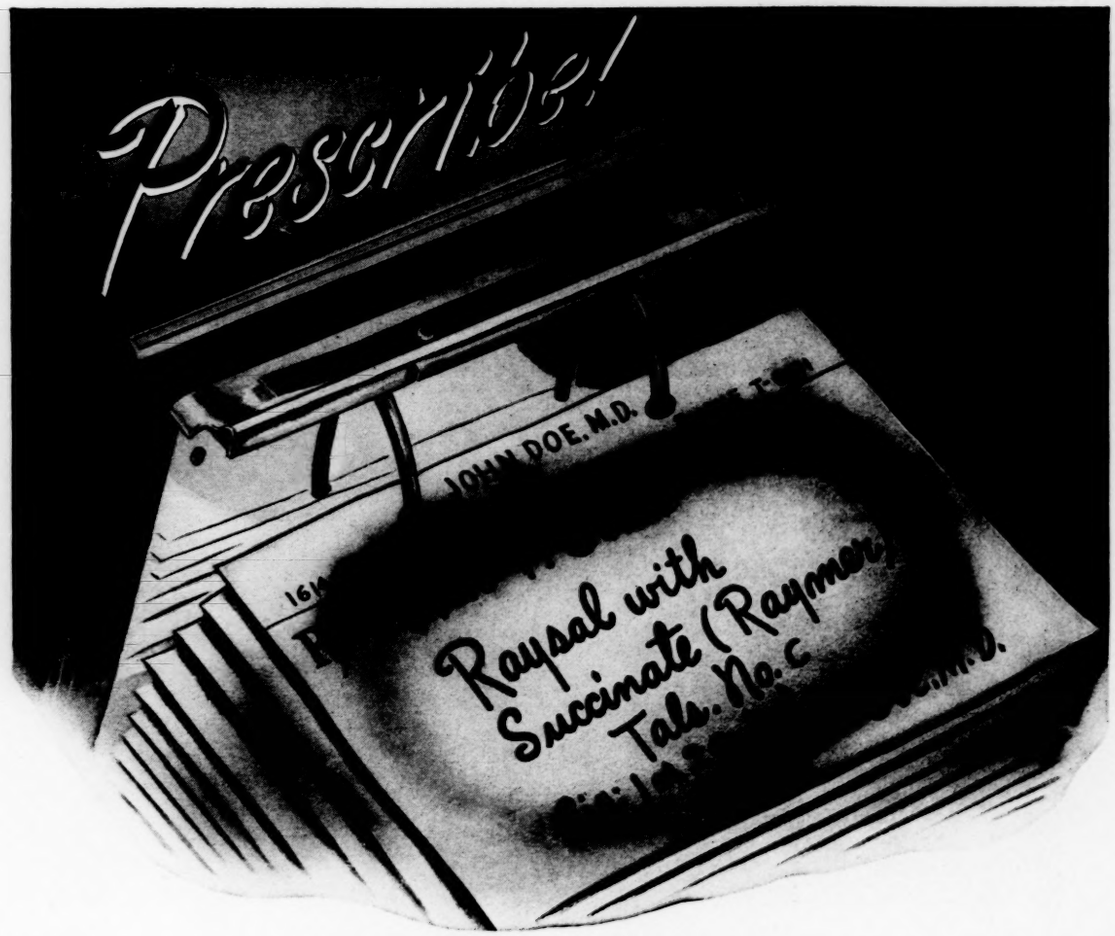
Delicious — **Eaten like cereal...may also be incorporated in cakes, biscuits, and waffle batters.**

Excellent Tolerance — **An extra 50 to 100 grams of protein daily easily administered.**

SUPPLIED: In 1-lb. packages, available through your local pharmacist.

*Exclusive trademark of Walker Vitamin Products, Inc.

Walker VITAMIN PRODUCTS, INC., MOUNT VERNON, N. Y.



for the Treatment of

ARTHRITIS and RHEUMATISM

RAYSAL WITH SUCCINATE . . . The *ethical* salicylate-succinate formula . . . Employs three principal ingredients—salicylate, iodine, and succinate . . . designed to combine the almost specific antiarthritic and antirheumatic action of the salicylates, the stimulating and nutritionally corrective effects of iodine and the salicylate detoxifying action of succinic acid.

An ideal companion medication for other therapeutic measures employed in arthritis and rheumatism. RAYSAL WITH SUCCINATE will enhance the efficiency of RAYFORMOSIL . . . a safe and effective combination for use in your next case. Sample and literature will be sent upon request.

The Detoxified Salicylate Medicament

ENTERIC COATED TABLETS (SALOL)

Raysal.....5 grains
(Representing 43% Salicylic Acid and 3% Iodine in Calcium-Sodium Phosphate Buffer Salt Combination)
Succinic Acid.....2 grains

RAYMER

Available for office use and at your pharmacy on prescription

PHARMACAL COMPANY • PHILADELPHIA 34, PA.
PHARMACEUTICAL MANUFACTURERS
Over a Quarter Century Serving Physicians

NOT ONLY FOR MEN

Androgenic hormone, despite its name, is not limited to the male sex, for it is present in appreciable amounts in the female where it is presumed to be necessary for the normal physiology of women. Moreover, it is not, strictly speaking, only a sex hormone, for its metabolic effects are considerable, particularly as regards protein anabolism. It has valuable therapeutic action in a variety of conditions which can be effectively and economically obtained with the ORETON preparations.

ORETON* (Schering's Testosterone Propionate U.S.P. XIII in ampuls and in vials for intramuscular injection)

ORETON Buccal Tablets (Schering's Testosterone Propionate U.S.P. XIII in POLYHYDROL base for buccal administration)

ORETON-M* (Schering's Methyltestosterone U.S.P. XIII in tablets)

ORETON-M Ointment (Schering's Methyltestosterone U.S.P. XIII ointment)

ORETON-F* (Schering's free testosterone in pellets for subcutaneous implantation)

have been successfully employed in men for eunuchoidism and the male climacteric; in women for metrorrhagia and dysmenorrhea; and in children for prematurity and dwarfism.

Packaging

ORETON—1 cc. ampuls containing 5, 10 or 25 mg.; boxes of 3, 6 and 50 ampuls. Multiple dose vials of 10 cc., 25 or 50 mg. per cc.; box of one vial.

ORETON Buccal Tablets—5 mg.; boxes of 30 and 100 tablets.

ORETON-M Tablets—10 mg.; boxes of 15, 30 and 100 tablets; 25 mg.; boxes of 15 and 100 tablets.

ORETON-M Ointment—Tube of 50 Gm.; 2 mg. per Gm.

ORETON-F Pellets—75 mg. pellet in individual vials; boxes of 1 and 3 vials.

POLYHYDROL trade-mark of Schering Corporation *®

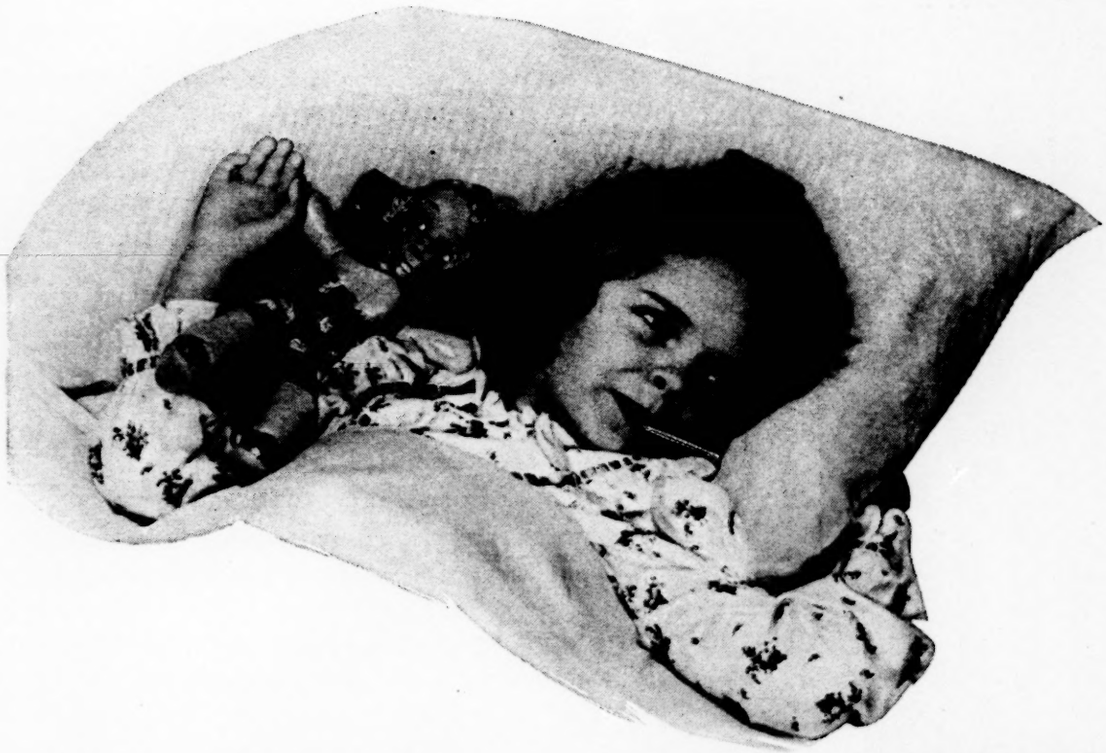
Schering

CORPORATION • BLOOMFIELD, NEW JERSEY

IN CANADA, SCHERING CORPORATION LTD., MONTREAL

SCHERING

ORETON



Young Patients Also Appreciate Pyridium®

GRATIFYING RELIEF *through effective, Safe Urogenital Analgesia*

DISTRESSING symptoms of urinary tract infection such as urinary frequency, pain and burning on urination can be relieved promptly in a high percentage of patients through the simple procedure of administering Pyridium orally.

Pyridium is virtually nontoxic in therapeutic dosage and can be administered concomitantly with streptomycin, penicillin, sulfonamides, or other specific therapy.

With this easy-to-administer and *safe* urinary analgesic, physicians can often provide their patients with almost immediate relief from distressing urinary symptoms during the time that other therapeutic measures are directed toward alleviating the underlying condition.

Literature on request

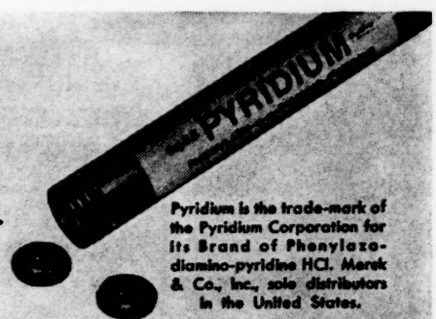
PYRIDIUM®

(Brand of Phenylazo-diamino-pyridine HCl)

MERCK & CO., Inc. RAHWAY, N. J.

Manufacturing Chemists

In Canada: MERCK & CO., Ltd. Montreal, Que.



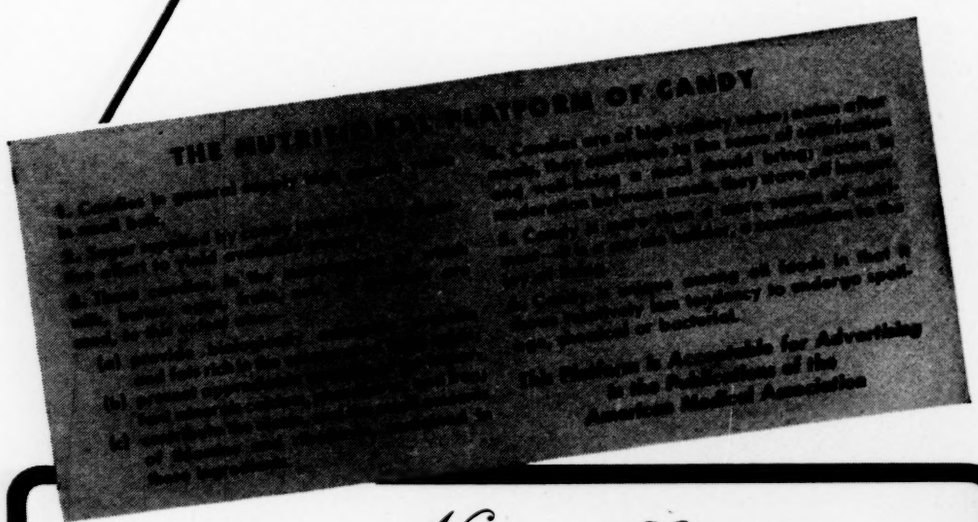
Pyridium is the trade-mark of the Pyridium Corporation for its Brand of Phenylazo-diamino-pyridine HCl. Merck & Co., Inc., sole distributors in the United States.

THE PLACE OF *Candy* IN THE *Balanced Diet*

In a carefully chosen, well balanced dietary providing all essential nutrients in proper amounts, there is adequate provision for foods which do more than merely satisfy nutrient needs—foods which are especially tempting to the palate. Candy is that kind of food.

Supplying valuable caloric food energy, it also imparts to a meal a finishing touch of which few other foods are capable. Candy, with its almost irresistible attraction, need not be denied children or adults providing the dietary is adequate in all other respects. In fact, candy at the conclusion of a meal imparts a feeling of satiety and a sense of having eaten well, both of which enhance the functioning of the digestive processes.

Many candies are made of valuable foods in addition to sugar—butter, milk, cream, eggs, nuts and peanuts—and to the extent these foods are present, candies contribute biologically adequate protein, vitamins, and minerals.



COUNCIL ON CANDY OF THE *National Confectioners' Association*

1 NORTH LA SALLE STREET CHICAGO 2, ILLINOIS

spoonfed

For your discriminating choice of a spasmolytic agent, these striking characteristics of Robins' Donnatal Elixir are particularly noteworthy:

- It's a superior spasmolytic in the most varied manifestations of visceral vagotonia—it suits the youngest, oldest, or the most finicky "taste."
- It provides the principal *natural* belladonna alkaloids in unvarying optimal ratios—is compatible with many adjuvant medications.
- It comprehensively combines peripheral and central sedation—for cases of either [illegible]genic or psychogenic etiology.
- It's potent spasmolysis . . . **spoonfed!**

Each 5cc of Donnatal Elixir contains:
Hyoscyamine Sulfate . . . 0.1037 mg.
Atropine Sulfate . . . 0.0194 mg.
Hyoscine Hydrobromide . . . 0.0065 mg.
Phenobarbital (¼ gr.) . . . 16.2 mg.

donnatal elixir

Also available as Donnatal Tablets and Donnatal Capsules

Robins

A. H. Robins Co., Inc.

Ethical Pharmaceuticals of Merit since 1878

Richmond 20, Va.

[illegible] READILY ACCEPTED SPASMOLYTIC THERAPY

in

water-soluble

vitamin

therapy

"aim above the mark to hit th[e]

"Err on the side of giving an exces[s] rather than giving too little," urges Jolliffe on vitamin supp[le]mentation. Says Spies: "[Pre]scribe it] too soon rather tha[n] late."[2] • In one small capsule, 'Robins' Allbee with C delivers the B-factors in two to fifteen times the minimum daily requirement* plus vitamin C [in] times the minimum daily requirement • Unmistakably, Allbee with C provides a ready means for water-soluble vitamin "saturation" therapy.

*or other official recommendations.

each capsule contains:

Thiamine Hydrochloride (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Calcium Pantothenate	10 mg.
Nicotinamide	50 mg.
Ascorbic Acid (C)	250 mg.

1. Jolliffe, N.: [illegible] New York [illegible] 41:1263, 19[illegible]
2. Spies, T. D. [illegible] J.A.M.A. 122:289, 19[illegible]

A. H. Robins Co., Inc. Richmond 20, Va.

ETHICAL PHARMACEUTICALS OF MERIT SINCE 1878

allbee C Robins

all th[illegible] water-[illegible]amins

Old Age NEED NOT MEAN *Chronic Illness*

Clinical studies[1,2,3] demonstrate that the results of inadequate dietaries are insidiously cumulative and may not become evident for many years. Many of the afflictions of old age are now attributed to lifelong faulty dietaries and no longer need be the inevitable accompaniment of advanced years.

In advanced age the wisdom of dietaries high in vitamins, minerals, and protein, low in fat, and moderate in carbohydrate, is pointedly emphasized in reported clinical studies. Liberal amounts of vitamin B complex and of calcium, in particular, are important for increasing the appetite and for supporting the calcium integrity of the skeletal structure.

Ovaltine in milk, a delicious *multiple* dietary supplement, is highly useful in the management of aged patients. Its multiple vitamins, its important minerals, and its biologically complete protein are the very nutrients required for effecting full adequacy of even seriously faulty diets. The refreshing tastefulness and easy digestibility are welcomed by the aged.

The rich dietary contribution made by three daily glassfuls of Ovaltine in milk, is outlined in detail in the table.

---

[1] Boss, E.P.: The Physiologic and Clinical Phenomena of Aging, New Orleans M. & S. J. 97:64 (Aug.) 1944.

[2] Spies, T.D., and Collins, H.S.: Observation on Aging in Nutritionally Deficient Persons, J. Gerontol. *1*:33 (Jan.) 1946.

[3] Stieglitz, E.J.: Therapy of the Aged, M. Ann. District of Columbia *17*:197 (Apr.) 1948.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES	676	VITAMIN A	3000 I.U.
PROTEIN	32 Gm.	VITAMIN B_1	1.16 mg.
FAT	32 Gm.	RIBOFLAVIN	2.0 mg.
CARBOHYDRATE	65 Gm.	NIACIN	6.8 mg.
CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN D	417 I.U.
IRON	12 mg.	COPPER	0.5 mg.

***Based on average reported values for milk**

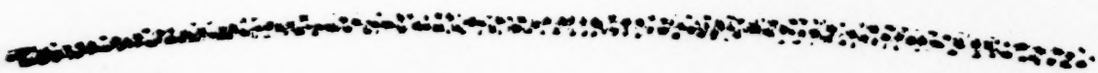
This penicillin-vasoconstrictor combination provides—

rapid and prolonged shrinkage

Par-Pen contains 'Paredrine Aqueous'—one of only two proprietary aqueous vasoconstrictors favorably noted in a report issued for the information of the Mayo Clinic Staff.

potent antibacterial action

Par-Pen contains sodium crystalline penicillin, now recognized as the most desirable form of this potent drug. An important advantage of this new form of penicillin is its superior stability. *Your patient need not refrigerate Par-Pen.* Even after a week at room temperature, Par-Pen will contain 500 units of penicillin per cc.—the accepted strength for local use. For samples and full information, write Par-Pen on your prescription blank and mail it to us at 1530 Spring Garden St., Philadelphia 1, Pa.



for intranasal use

Smith, Kline & French Laboratories, Philadelphia

Now! CHLOROPHYLL* AEROSOL THERAPY

the new advance in the Inhalation Treatment of Respiratory Tract Infections

CHLOROPHYLL AEROSOL THERAPY, as made possible by *Chloresium Aerosol Solution, enables the physician to provide the remarkable therapeutic effectiveness of chlorophyll in the inhalation treatment of both upper and lower respiratory tract infections. It is the result of intensive laboratory and clinical investigation to meet the long-felt need for an effective nontoxic, healing, decongestive, antibacterial and deodorizing agent for use in inhalation therapy.

For use with any standard nebulizing equipment

Chloresium Aerosol Solution is a specially processed preparation containing the purified therapeutically active *water-soluble* derivatives of chlorophyll "a" ($C_{55}H_{72}O_5N_4Mg$), designed for use with any standard nebulizing equipment. It is a natural, nontoxic, biotherapeutic agent and may be used either alone or, where indicated, as a solvent vehicle for penicillin or other antibiotic inhalation therapy.

A unique combination of advantages

Chloresium Aerosol Solution provides the following unique and fundamental advantages in inhalation therapy:

Absolutely nontoxic
Accelerates healing by stimulating normal cell metabolism
Decongests, promptly, without rebound phenomena
Exerts antibacterial effect, particularly on secondary saprophytic, proteolytic invaders
Does not interfere with ciliary activity; tends to restore normal motility if impaired
Can be used freely—especially valuable in the field of pediatrics
Deodorizes fetid, foul-smelling conditions
May be used as solvent vehicle for antibiotic inhalation therapy

Indicated for all respiratory tract infections

The value of Chloresium Aerosol Solution used alone or as vehicle for antibiotics has been demonstrated in the treatment of most infections of the respiratory tract including acute and chronic sinusitis, rhinitis, pharyngitis, ordinary coryza, ozena, acute and chronic laryngitis, bronchitis, bronchiectasis, lung abcesses and other deep-seated inflammatory conditions.

Chloresium
Aerosol Solution

ETHICALLY PROMOTED
Available at all leading drugstores

FREE—MAIL COUPON

RYSTAN CO., INC., Dept. JM-2
7 N. MacQuesten Parkway
Mt. Vernon, N. Y.

Please send me, without obligation, clinical samples of Chloresium Aerosol Solution and complete literature.

Dr._____

Address_____

City_____ Zone____ State_____

Coming!

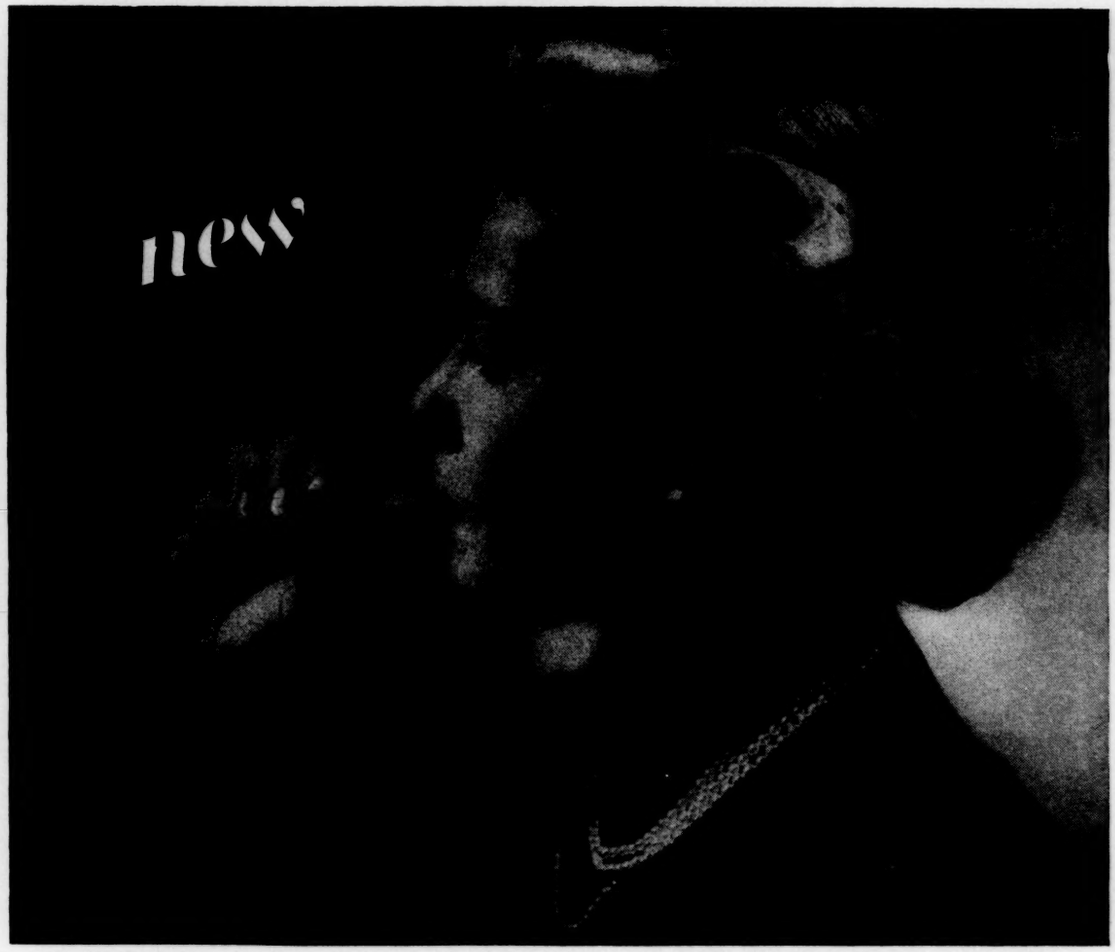
SYMPOSIUM ON

POLIOMYELITIS

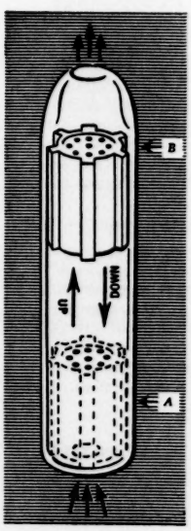
Guest Editor

John R. Paul, M. D.

YALE UNIVERSITY SCHOOL
OF MEDICINE



Simplicity IN PENICILLIN POWDER INHALATION THERAPY



'DISPOLATOR' IS A TRADEMARK OF E. R. SQUIBB & SONS

Inhalations draw container A to point B, where penicillin powder enters the air stream.

Disposable After treatment, the patient throws it away.

Easy to use The Dispolator is a complete therapeutic unit. The patient has no assembly problems.

Effective Can be inhaled through mouth or nostrils. Maximum concentration of penicillin per unit area. Slower absorption for longer topical action.

Economical Nothing else to buy.

Supplied in Packages of 3.

PENICILLIN DISPOLATOR

SQUIBB micro-pulverized penicillin inhaler (DISPOSABLE)
100,000 units crystalline penicillin G sodium

SQUIBB

Supplement Restricted Diets

Sore tongue, undue fatigue, skin eruptions, neuritis—all these symptoms may indicate a deficiency caused by a necessarily limited diet. This deficiency is due to the fact that the body has very little storage capacity for the B Complex vitamins.

B Complex Preparations Armour

can protect the patient from developing this deficiency by providing adequate vitamin therapy.

Have confidence in the preparation you prescribe—specify "Armour"

ARMOUR Laboratories

ARMOUR B COMPLEX PREPARATIONS

ARMOUR THERAPEUTIC B COMPLEX TABLETS

Each tablet contains:

Secondary Liver Fraction	0.6 gram
Thiamine Hydrochloride	10.0 milligrams
Riboflavin	20.0 milligrams
Pyridoxine HCl (Vitamin B_6)	0.5 milligrams
Calcium Pantothenate	5.0 milligrams
Niacinamide	150.0 milligrams

Suggested dose: One tablet per day or as directed by physician. Available in boxes of 100 tablets.

ARMOUR B COMPLEX HIGH POTENCY CAPSULETTES

Each capsulette contains at least:

Secondary Liver Fraction	0.4 gram
Thiamine Hydrochloride	2.0 milligrams
Riboflavin	4.0 milligrams
Pyridoxine HCl (Vitamin B_6)	0.25 milligrams
Calcium Pantothenate	2.5 milligrams
Niacinamide	20.0 milligrams

Suggested dose: One to two capsulettes three times a day at mealtime or as directed by physician. Available in boxes of 100 capsulettes.

ARMOUR B COMPLEX CONCENTRATE (LIQUID)

Each fluid drachm (one teaspoonful) contains at least:

Vitamin B_1 (Thiamine Hydrochloride)	0.450 milligram
Vitamin B_2 (Riboflavin)	80.0 micrograms
Nicotinic Acid	1.250 milligrams
Liver Extract and Yeast Concentrate	200.0 milligrams

(Derived from 8 grams fresh liver and 0.2 grams fresh yeast.)
Suggested dose: One to two teaspoonfuls three times a day or as directed by physician. Available in 8 oz. bottles.

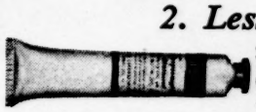
Streptomycin *is now available in* Ointment *form*

Here is another original contribution to the antibiotic armamentarium from Bristol Laboratories: streptomycin sulfate for topical application, in a smooth, greaseless, ointment base. This significant development of Bristol research is noteworthy for the following:

1. A Broad Antibacterial Spectrum

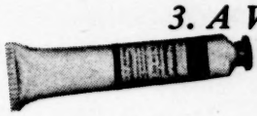
The variety of bacteria destroyed or inhibited by streptomycin is remarkably broad. Its antibacterial spectrum surpasses those of other antibiotics in current use for topical application.

2. Less Sensitizing



Streptomycin in ointment form minimizes the greatest single objection to topical antibiotic therapy in that it is demonstrably less sensitizing.

3. A Water-Soluble Ointment Base



Bristol Streptomycin Ointment is unusually pleasant to use, because it is incorporated in a smooth, water-soluble base. Despite the fact that there is no grease or oil, adequate potency can be expected to persist throughout the full dating period of nine months after manufacture.

Bristol STREPTOMYCIN OINTMENT is indicated in skin and wound infections due to streptomycin-sensitive organisms. Each gram of the ointment contains 5000 micrograms of pure streptomycin.

Available NOW from your usual source of supply, in 1 oz. tubes, singly, or packed 12 to a carton.

Bristol
LABORATORIES INC.
SYRACUSE, NEW YORK

Tyrothricin

Benzocaine

ANTIBIOTIC-ANESTHETIC
THROAT LOZENGES

Tyrothricin, potent antibacterial extract of Dubos' bacillus, and widely considered the topical antibiotic of choice, is the principal ingredient of TYROZETS Lozenges, Sharp & Dohme's remarkable new preparation for prophylaxis and treatment of gram-positive throat and mouth infections, and for post-surgical care of the pharynx.

Tyrothricin is penetrating, nontoxic when applied locally, and highly effective against such gram-positive organisms as Corynebacterium diphtheriae, pneumococci, streptococci and staphylococci frequently responsible for infections of throat and mouth.

Each TYROZETS lozenge contains tyrothricin, 1 mg., and 5 mg. of soothing, analgesic benzocaine.

TYROZETS Antibiotic-Anesthetic Throat Lozenges rapidly relieve the pain and discomfort of infected or irritated throats, promptly destroying gram-positive pathogens. These new, nontoxic, pleasantly flavored Sharp & Dohme lozenges are indicated for treatment of gram-positive throat and mouth infections, sore throats, and especially following tonsillectomies and pharyngeal surgery. They are also effective for prophylactic throat protection when colds are prevalent.

TYROZETS Lozenges are packed in neat, shatter-proof, amber plastic tubes of 12. Sharp & Dohme, Philadelphia 1, Pa.

SHARP & DOHME **TYROZETS**

HIGH POTENCY ASSURED IN *Kinney's* FORTIFIED YEAST PRODUCTS

FORTIFIED YEAST EXTRACT—KINNEY provides potent B-complex therapy in a palatable, readily absorbed form. It is a highly concentrated aqueous extract of specially cultured yeast, containing the whole vitamin B complex, fortified with important crystalline B factors.

One teaspoonful three times daily supplies thiamine, riboflavin, and niacin in amounts adequate for the correction or prevention of deficiencies.

AVAILABLE in bottles of 4 fl. oz. and 1 pt.

For convenience when traveling or at work,
FORTIFIED YEAST TABLETS—KINNEY

Provide the whole B complex as present in yeast, fortified with crystalline B factors.

Two tablets two or three times daily for prevention or correction of thiamine, riboflavin, or niacin deficiencies.

AVAILABLE in bottles of 100 and 1,000 tablets of 5 grains each.

Kinney®

KINNEY & COMPANY
COLUMBUS INDIANA

The Abundant Nutrient Values of MEAT

KIND OF MEAT	COMPLETE PROTEIN	B VITAMINS			FOOD IRON
		THIAMINE (B_1)	RIBOFLAVIN (B_2)	NIACIN	
 PORK	EXCELLENT	EXCELLENT	FAIR	EXCELLENT	EXCELLENT
 BEEF	EXCELLENT	FAIR	EXCELLENT	EXCELLENT	EXCELLENT
 LAMB	EXCELLENT	FAIR	GOOD	EXCELLENT	EXCELLENT
 VEAL	EXCELLENT	GOOD	GOOD	EXCELLENT	EXCELLENT
 VARIETY MEATS (LIVER, HEART, KIDNEY)	EXCELLENT	EXCELLENT	EXCELLENT	EXCELLENT	EXCELLENT
 SAUSAGE (FRANKFURTERS, BOLOGNA)	EXCELLENT	GOOD	GOOD	GOOD	EXCELLENT

ALL VALUES ARE BASED ON COOKED MEATS MEAT ALSO SUPPLIES SIGNIFICANT AMOUNTS OF COPPER AND PHOSPHORUS

While its high content of biologically complete protein ranks meat among man's best protein sources, its contribution of many more indispensable nutrients further enhances its over-all desirability in the daily dietary.

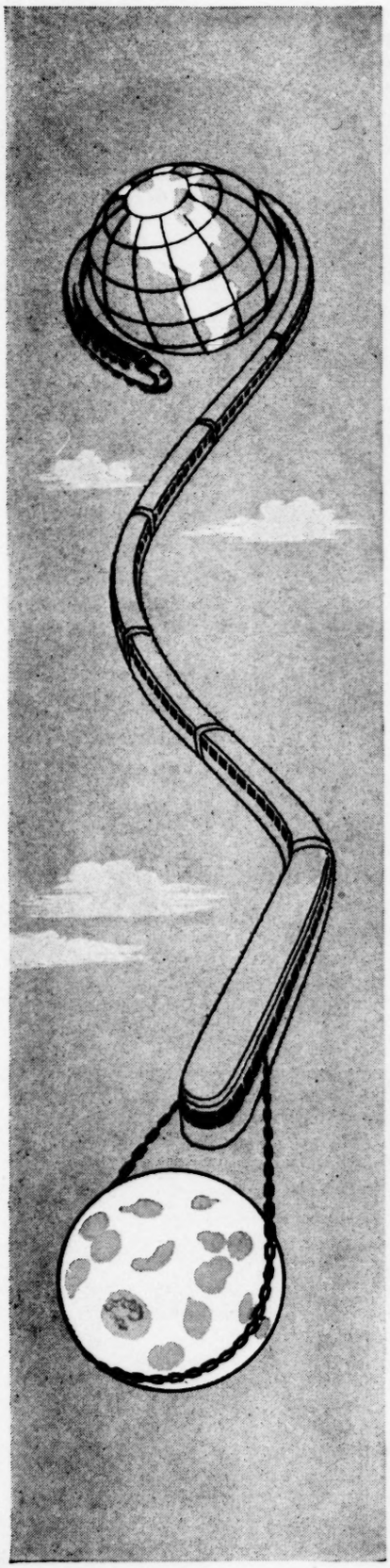
As is readily seen in the chart above, every kind of meat is an excellent source of high quality protein and of iron. Meat further supplies significant amounts of the three B complex vitamins, thiamine, riboflavin and niacin. Certain cuts and kinds of meat are, as a matter of fact, among our richest food sources of thiamine and niacin. All meat, regardless of grade or cut, makes these contributions.

Due to the excellent digestibility of meat—from 96 to 98 per cent—the metabolic availability of its protein and other nutrients is virtually assured, making it particularly valuable in many disease conditions in which these nutrients are especially needed.

AMERICAN MEAT INSTITUTE

Main Office, Chicago . . . Members Throughout the United States

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



Slow-Down Strike on the Blood Transit

ENOUGH CORPUSCLES IN THE
BODY TO STRETCH FOUR TIMES
AROUND THE GLOBE—
A BLOOD TRANSIT SYSTEM—
AND WHEN HEMOGLOBIN IS DOWN
THERE'S A "POWER LEAKAGE"
WITH SECONDARY EFFECTS—
ANOREXIA, AVITAMINOSIS
AND ACHLORHYDRIA.

Watch out for those secondary effects in the secondary anemias

HEPTUNA with folic acid

meets all these needs in a single capsule. Study the formula. Clinical observation shows HEPTUNA with Folic Acid brings a rapid hemoglobin regeneration, change in the hematopoietic picture and relief of secondary effects with a minimum of digestive reactions.

ALL IN ONE CAPSULE

Folic Acid	*1.7 mg.*
Ferrous Sulfate U.S.P.	*4.5 Grains*
Vitamin A (Fish-Liver Oil)	*5,000 U.S.P. Units*
Vitamin D (Tuna-Liver Oil)	*500 U.S.P. Units*
Vitamin B_1 (Thiamine Hydrochloride)	*2 mg.*
Vitamin B_2 (Riboflavin)	*2 mg.*
Vitamin B_6 (Pyridoxine Hydrochloride)	*0.1 mg.*
Calcium Pantothenate	*0.333 mg.*
Niacinamide	*10 mg.*

Together with other B-complex factors from liver and yeast

ONE OF THE ROERIG BALANCED FORMULAE

PHARMACEUTICALS ROERIG

Originators of HEPTUNA • DARTHRONOL • OBRON

J. B. ROERIG AND COMPANY
536 LAKE SHORE DRIVE • CHICAGO 11, ILLINOIS

PENICILLIN POWDER INHALATION

As simple as...

Inhale—Remove—Exhale... that's all there is to penicillin powder inhalation with the Aerohalor. This inexpensive little device is motivated by the patient's respiration. It is used with disposable Abbott Sifter Cartridges which contain 100,000 units of finely powdered crystalline penicillin G sodium. Each Aerohalor has an interchangeable mouthpiece and nosepiece for oral and nasal inhalation. The device may be prescribed for use at home, work or in your office. This form of treatment is indicated in infections of the upper or lower respiratory tract susceptible to penicillin. It is contraindicated in infections not susceptible to penicillin and for patients allergic to the drug. No serious reactions have been reported. Your pharmacy can supply the Aerohalor and Abbott Sifter Cartridges, the latter on prescription only. For descriptive literature, write ABBOTT LABORATORIES, North Chicago, Illinois.

HOW IT WORKS: As patient inhales, air enters curved intake tube causing metal ball to strike cartridge containing penicillin powder. This shakes limited amount of powder into stream of air, where it is carried to respiratory passages, absorbed into bloodstream.

AEROHALOR
TRADE MARK
Abbott's Powder Inhaler

a new and outstanding development in penicillin therapy

PENICILLIN S-R*

Parke-Davis

COMBINED SOLUBLE AND REPOSITORY PENICILLIN

higher initial levels

A 1-cc. intramuscular injection produces serum levels of 4.0 units per cc.—a value 133 times higher than the commonly accepted therapeutic level, 0.03 units per cc.

quicker maximal therapeutic levels

Within a half hour or less after the injection, a high concentration of penicillin is found in the tissues.

prolonged high maintenance levels

For twenty-four hours or longer, a single injection continues to provide effective therapeutic levels.

better control of infection

Rapid onset and prolonged maintenance of higher levels means more effective antibacterial action than possible with penicillin in retardant vehicles.

extra margin of effectiveness

Higher levels quickly obtained permit early dominance over infecting organisms and diminish likelihood of penicillin-fastness.

ease of flow

Penicillin S-R contains no oil, no wax, no added suspending or dispersing agents to impede injection or clog needle and syringe.

additional advantages of **PENICILLIN S-R**

PREPARATION:	ADMINISTRATION:	CONVENIENCE:	TOLERANCE:
Easily and quickly prepared	Free-flowing	Syringe and needle need not be dry	No sensitizing diluents
Aqueous diluent	Quickly injected	No plugging of needles (20 or 21 gage)	No added suspending agents
No vigorous shaking	No special-type syringe	Syringe and needles easily cleaned	Completely absorbed
			Minimal pain

PENICILLIN S-R is supplied in both one-dose (400,000 units) and five-dose rubber-diaphragm-capped vials. When diluted according to directions (with Water for Injection, U.S.P., Normal Saline Solution, U.S.P., or 5 per cent Dextrose Injection, U.S.P), each cc. contains 300,000 units of crystalline procaine penicillin-G and 100,000 units of buffered crystalline sodium penicillin-G. The one-dose vial is also available with an accompanying ampoule of Water for Injection, U.S.P., if desired. Potency of the suspension is maintained for seven days at refrigerator temperatures.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

MEDICAMENTA VERA · PD & CO.

*Trademark

wes·sal
MARK

the only salt substitute that tastes exactly like salt

wes·sal** is a joy* to patients on low-salt (sodium) diets. It's the *only* salt substitute that makes food taste *exactly* as if seasoned with salt. No bitter, no disagreeable taste. Used freely at the table—in cooking and baking. ● Sodium-free, safe, convenient, ***wes·sal assures eating without cheating, a minimum intake of harmful sodium, better nourishment, and grateful, happier, patients in . . .

congestive heart failure • hypertension • toxemias of pregnancy

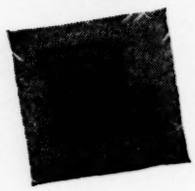
send for tasting samples →

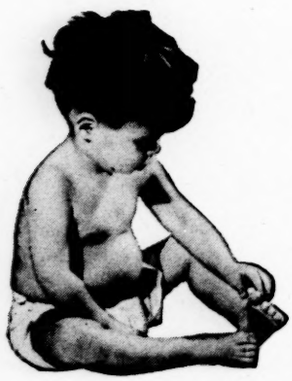
wes·sal is a solution of lithium chloride with small amounts of citric acid and potassium iodide (iodizing traces). Bottles of 2¼ oz.

WESTWOOD PHARMACEUTICALS, Dept. AJM ● 468 Dewitt St., Buffalo 13, N. Y.
division of Foster-Milburn Co.

five essentials

accounted for





If baby knew, as physicians do, the importance of adequate quantities of the five vitamins considered essential to good nutrition, he would count his vitamins even more carefully than his toes. For infants, one-half to one average teaspoonful of **HOMICEBRIN** (Homogenized Vitamins **A**, B_1, B_2, **C**, and **D**, Lilly) will provide the optimal requirements for these five vitamins.

Pleasantly flavored, HOMICEBRIN is miscible with water, milk, or orange juice. It is available in bottles of 60 cc. and 120 cc. at retail drug stores everywhere.

ELI LILLY AND COMPANY

The American Journal of Medicine

VOL. VI FEBRUARY, 1949 No. 2

Editorial

Coronary Failure and Coronary Arteritis

EVERY doctor is thoroughly familiar with the clinical features of Heberden's angina pectoris as well as with those of acute coronary thrombosis with cardiac infarction. The peculiar paroxysmal precordial pain brought on by effort or emotion and relieved by rest or by nitroglycerin in the former, and the steady and prolonged distress often associated with shock, requiring morphine and not relieved by vasodilators in the latter, usually lead to easy and certain diagnosis. Less well understood, however, are those syndromes which seem to occupy an intermediate position between typical angina and cardiac infarction. A patient, usually with a known background of coronary disease, experiences bouts of precordial, substernal or arm pain often coming on at rest and not necessarily after exercise or after any obvious emotional aggravation. Such attacks may last for hours or days; they are not adequately relieved by nitrites and yet there is no definite evidence of cardiac infarction. In the type of case to which we allude there is no fever, leukocytosis, alteration in sedimentation rate or progressive electrocardiographic change in association with the bout of pain. Now this is clearly not typical Heberden's angina in the sense of a transitory anoxia or ischemia of the heart muscle, nor does it seem probable that episodes of such prolonged grumbling pain, repeated perhaps a number of times during a period of days or weeks, could correspond to an equal number of distinct coronary thromboses or cardiac infarctions.

In a recent paper Freidberg, Blumgart, Zoll and Schlesinger[1] discuss the problem of these syndromes more or less intermediate between angina pectoris and cardiac infarction. Autopsies are reported in a number of patients which show ample evidence of coronary disease—arteriosclerosis, old and fresh coronary thromboses, ulceration of atheromatous plaques—but no accurate correlation between the bouts of pain which the patient had experienced and the evidences of infarction was possible. The writers give it as their opinion that pain in these cases is essentially of the same nature as that occurring in the other coronary syndromes. They believe that the distress is due to a relative anoxia of heart muscle. This is presumed to lead to the accumulation of metabolic products which in turn act on pain nerve endings in the heart, especially in the vessels. The absence of evidence of infarction by clinical tests and perhaps at autopsy as well is explained by the presumption that the ischemia is not of sufficient degree to cause actual death of a portion of heart muscle. The term "coronary failure" is endorsed by Freidberg and his associates as an appropriate designation for these "intermediate" coronary syndromes.

It seems of interest, however, to consider a different explanation for the pain in some of these cases, namely, the possibility that it may arise directly from a lesion in the vessel wall. That an injury to the arterial

[1] FREIDBERG, A. S., BLUMGART, H. L., ZOLL, P. M. and SCHLESINGER, M. J. Coronary failure. *J. A. M. A.*, 138: 107, 1948.

wall gives pain one can readily convince himself of by having a puncture of his radial artery done without anesthesia and with a dull needle. An exquisite attack of anginal distress in reverse is produced; the pain radiates up the arm to the precordium. Pain arising directly from disease of arterial walls is also to be seen with a split in the aorta such as occurs in cases of dissecting aneurysm, with syphilitic aneurysm and perhaps in certain diseases of the peripheral arteries. Experimentally also the ingenious observations of Gorham and his associates[2] showed that pain can be produced by tridirectional traction on the wall of a coronary artery, without evident narrowing of the lumen and without electrocardiographic changes. Katz[3] also pointed out that occlusion of carefully isolated strips of coronary artery in the dog yielded no evidence of pain nor did pain result from the crushing of arterial strips in which the nerves had been destroyed by phenol. In brief, then, one wonders whether in some of these patients with prolonged "coronary" pain not anginal in type and without evidence of cardiac infarct the distress may not, in part at least, arise directly from a lesion in the vessel wall rather than wholly as the result of myocardial ischemia. One may suggest the possibility that in a person who has coronary disease, hemorrhage into the vessel wall or some progression or alteration in an atherosclerotic patch could directly cause the artery to become painful, that such pain could come and go over variable periods of time, that nitrites would not be expected to relieve whereas morphine would, and that evidences of infarction and striking electrocardiographic changes would not be anticipated. Furthermore, the sequence of events often seen, of precordial aching later followed by full evidence of thrombosis and infarct may be explained by the fact that a painful lesion in the vessel wall finally comes to the internal surface with formation of intra-arterial clot. Blumenthal and Reisinger[4] have suggested that intramural hemorrhage under these conditions may provoke pain by tension on the adventitia. Still further evidence that pain may arise in arteries is presented by Wolff[5] in his monograph on headache.

If it should turn out that certain types of coronary pain arise directly from a lesion in the vessel wall, *coronary arteritis* would seem to be a simple designation even if not an entirely accurate one. Perhaps a better term could be found. No doubt both "coronary arteritis" and coronary failure could contribute to the clinical phenomena in various cases, and further work would be necessary to evaluate the relative importance of these components in the individual. The matter is not one of academic interest alone but has a very practical side in the planning of treatment. If pain is caused early by a lesion still confined to the interior of the vessel wall, dicumarol might be invaluable in preventing coronary thrombosis from occurring later, and indeed might be of greater use than after frank occlusion and infarction have supervened. If on the other hand pain is due merely to disproportion between the coronary lumen and the need for blood on the part of the myocardium, there would be less immediate indication for anticoagulant therapy.

ARTHUR L. BLOOMFIELD, M.D.

[2] MARTIN S. J. and GORHAM, L. W. Cardiac pain: An experimental study with reference to the tension factor. *Arch. Int. Med.*, 62: 840, 1938.

[3] KATZ, L. N., MAYNE, W. and WEINSTEIN, B. S. Cardiac pain: presence of pain fibers in the nerve plexus surrounding the coronary vessels. *Arch. Int. Med.*, 55: 760, 1935.

[4] BLUMENTHAL, B. and REISINGER, J. A. Prodromal pain in coronary occlusion. *Am. Heart J.*, 20: 141, 1940.

[5] WOLFF, HAROLD, G. Headache and Other Pain. New York, 1948. Oxford University Press.

Clinical Studies

Multiple Myeloma*

Its Clinical and Laboratory Diagnosis with Emphasis on Electrophoretic Abnormalities

W. S. Adams, M.D., E. L. Alling, M.D. *and* J. S. Lawrence, M.D.†

Rochester, New York

This report deals with the clinical and laboratory findings in sixty-one cases of multiple myeloma. Particular emphasis has been placed on the importance of the occurrence of electrophoretic abnormalities in this disease. It is hoped that a report of these findings will be useful to others in making an early and accurate diagnosis of multiple myeloma.

HISTORY

In 1845 a forty-seven year old grocer who had been "out of health for thirteen months" was seen by his physician, Sir James Watson. A peculiar substance which solidified on cooling was noted in the urine. Being curious as to the nature of this substance both Dr. Watson and Dr. MacIntyre, the latter having been called in consultation, sent samples of the urine to Henry Bence Jones.[1] After considerable study Bence Jones found that this unusual urinary substance precipitated on heating, cleared on boiling and returned to a solid state on cooling. He also noted at necropsy that the "bony structure of the ribs was cut with the greatest ease, and that the bodies of the vertebrae were capable of being sliced off with a knife." Bence Jones concluded from the chemical properties of this urinary substance that it was "an oxide of albumen, and from the ultimate analysis it is the hydrated deutoxide of albumen." He also suggested that this substance should be looked for in further cases of "mollities ossium" and prophesied that the explanation of its formation might lead to "the comprehension of the nature of the disease which affects the bones." This protein is now known as Bence Jones protein and the disease with which it is commonly associated, multiple myeloma. One year later, in 1846, Dalrymple[2] published an article on the "microscopical character of mollities ossium." In this article he described the gross appearance of the diseased bone, recognized the replacement of bone by "nucleated cells," and correctly suspected the malignant nature of the disease. In 1850 MacIntyre[3] reported at length the case of Watson and Bence Jones. His description of the symptomatology of the disease is as accurate today as it was almost 100 years ago. Von Rustizky[4] first described the condition under the name of "Multiple Myelome" in 1873 but it was not until 1889 that Kahler[5] ascribed the four cardinal findings to this disease, i.e. bone pain, deformation and abnormal fragility of bone, cachexia and the presence of Bence Jones proteinuria. Ten years later Ellinger[6] first noted the interrelationship of hyperproteinemia and multiple tumors of bone. This important work was corroborated by Jacobson[7] in 1917 and by many others since that time. Longsworth, Shedlovsky and Mac-

* From the Departments of Medicine and Radiology, University of Rochester School of Medicine and Dentistry, and the Medical Clinics of the Strong Memorial Hospital and the Rochester Municipal Hospital, Rochester, N. Y.
Expenses were defrayed in part by a grant from the American Cancer Society.
† Present address: Department of Medicine at the University of California at Los Angeles.

Innes[8] were the first to make electrophoretic studies in cases of multiple myeloma and pointed out the existence of unusual patterns in this condition.

INCIDENCE

Plasma cell tumors are rare but are probably not nearly so rare as they have been reported in the past. At this clinic they represented 0.02 per cent of all hospital admissions and 0.66 per cent of all malignancies. It is interesting to note that from 1926 to 1936 the incidence of multiple myeloma was 1.4 cases per 10,000 hospital admissions, and from 1936 to 1946, 2.8 cases per 10,000 hospital admissions. Doubtless this two-fold increase is due to a variety of causes perhaps the most significant of which has been the electrophoretic study of plasma proteins. More expert hematologic and pathologic examination of the blood and blood-forming tissues has also played a prominent part in this apparent increase. Then, too, greater numbers of people are entering the fifth, sixth and seventh decades of life than ever before and it is during these decades that myeloma is most common.

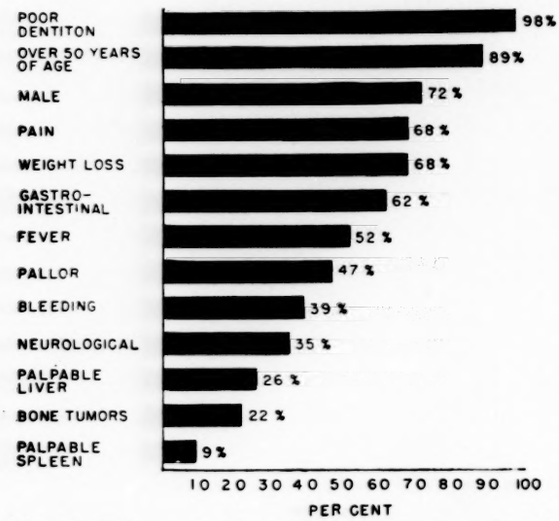


FIG. 1. Signs and symptoms of sixty-one cases of multiple myeloma.

CLINICAL FINDINGS

The signs and symptoms which were noted in sixty-one cases of multiple myeloma are summarized in Figure 1. They will be discussed in order of frequency.

Poor Dentition (98 per cent). Surprising as it may seem the commonest clinical finding was a pronounced carious condition or a complete absence of teeth. It is realized that the majority of normal people in this age group have either total or partial loss of teeth. However, it seems outside the realm of chance that practically all cases of multiple myeloma should show this unless there were some other factor which predisposed to dental softening. The purely speculative hypothesis is offered that the same process which so commonly leads to skeletal osteoporosis also affects the teeth and leads to their premature decay and removal.

Age. It is a well established fact that this disease is most prevalent in the older age groups. However, well authenticated cases have been reported in children and infants,[9] but these cases must be regarded as medical curiosities. The average age of patients with multiple myeloma in this group was fifty-eight years, 89 per cent of all patients being over fifty years of age at the time of admission to the hospital. The extremes of age were thirty-one and seventy-six years.

Sex. The male sex is more commonly affected than the female. The reasons for this are not clear. Bone trauma, to which the male is more often exposed, has been implicated as an important predisposing factor by some. In our experience the disease was seen two and one-half times more frequently in the male than in the female. The answer to this observed fact must await further investigation.

Pain (68 per cent). Any description of multiple myeloma would be incomplete without reference to the pain which commonly accompanies the disease. The pain is of two types: that due to bone pain *per se* and that due to fracture of bone. The bone pain may begin insidiously, sometimes being remittent in type resembling "rheumatic pains." These pains usually progress and terminate in agonizing spasms. The

latter are best described by those who have experienced them: "My muscles feel like they are being torn from my legs," and "It feels like a steel band is being tightened about my knee." Many patients have begged the examiner not to come near the bed for fear of bringing on agonizing paroxysms of pain. The cause of this pain is not clear. It is thought that the osteolytic process taking place in the medullary cavity of the bone is responsible.

In contradistinction to the insidious onset of this type of pain there may be a sudden onset of acute pain which is usually the result of a pathologic fracture incurred by a sudden movement or the lifting of a heavy object. This pain is frequently limited to the back or the chest and may be of such severity as to cause the patient to cry out or fall to the floor.

Weight Loss (68 per cent). Early in the course of multiple myeloma weight loss is usually slight. However, as the disease progresses and particularly if uremia develops, the loss of weight becomes pronounced (averaging 29 pounds). Our patients admitted to weight loss in 68 per cent of the cases in which an adequate history could be obtained. It is surprising to us that inanition is not more extreme in view of the excessive loss of protein in the urine shown by some of our cases.

Gastrointestinal Symptoms (62 per cent). Associated with weight loss have been varying degrees of anorexia, nausea, vomiting, diarrhea and constipation. As a rule these symptoms were not distressing unless azotemia developed when, as would be expected, anorexia, nausea and vomiting were often pronounced.

Fever (52 per cent). Fever is a common accompaniment of the disease. It is usually low-grade, remittent and resembles the febrile course sometimes seen in tuberculosis. Terminally, the fever may go as high as 40° to 41°C. This terminal hyperpyrexia cannot always be explained on the basis of pneumonia or other existing infection. Its etiology remains obscure.

PHYSICAL FINDINGS

Pallor (47 per cent). By the time they seek medical care the majority of patients with myeloma are already suffering from anemia of considerable severity. The pallor (present in 47 per cent of the cases) is many times associated with a peculiar, dusky, sallow coloration which cannot be attributed to anemia *per se*. This peculiar appearance of the skin is not distinctive of myeloma for it is often seen in other malignant states.

Bleeding (39 per cent). Hemorrhage from the nose, gums, lungs, gastrointestinal tract and into the skin has been reported previously. In the majority of these cases no known defect in the clotting mechanism has been implicated. This has been true in fifteen of our cases in which bleeding was encountered and in which adequate studies including fibrinogen level, prothrombin concentration, bleeding time and platelet counts were made. However, in five of these patients with marked hyperproteinemia the clot was very friable and retracted poorly. It has been suggested by Bayrd and Heck[10] that the abnormal bleeding tendency encountered in multiple myeloma may be explained on the basis of hyperproteinemia. Proof of this hypothesis must await further study.

It is important to note that in three of our patients in whom surgical procedures were carried out, profuse hemorrhage was encountered. We have no explanation of this.

Neurologic (35 per cent). Disorders of the nervous system are more commoner than one might expect. The majority of neurologic lesions in this group were an indirect result of pathologic fracture of the skeletal system. Because of the frequency of involvement of the vertebral column resulting in collapse of the vertebral bodies, root cord compression with its attendant root pain was the commonest neurologic manifestation.

Palpable Liver and Spleen. The liver and spleen were palpable in 26 and 9 per cent, respectively, of all cases. Much higher percentages have been reported but in these

cases the presence of a palpable liver or spleen was not very common.

Palpable Tumors (22 per cent). Rarely (three cases in this series) the presenting complaint was a palpable tumor attached to the bone. In general these tumors were

FIG. 2. Laboratory findings of sixty-one cases of multiple myeloma.

non-tender, soft, frequently pulsatile masses and were attached to the sternum, skull, ribs, clavicle or jaw.

LABORATORY FINDINGS

The laboratory findings in sixty-one cases of multiple myeloma are shown in Figure 2.

Bence Jones Protein. Despite the fact that over 100 years ago Watson, Dalrymple, MacIntyre and Bence Jones noted a peculiar urinary protein in a patient with multiple myeloma, we still know little about the origin or the physiology of this protein. Wintrobe and Buell[11] point out that "Bence Jones protein must be regarded as a class of substances which exhibit in common a peculiar coagulation phenomenon."

The incidence of Bence Jones proteinuria in cases of multiple myeloma is a matter of extreme variation as reported in the literature:

Name	Per cent
Atkinson[12]	87
Magnus-Levy[13]	73
Geschickter and Copeland[14]	65
Bayrd and Heck[10]	53
Batts[15]	50
This report	47
Gutman[25]	45
Ghormley and Pollock[16]	35
Coley[17]	8

As can be seen above the incidence of Bence Jones proteinuria in our series was 47 per cent. The marked variation in incidence of Bence Jones proteinuria is understandable when one considers the nature of this substance or substances. It has been pointed out[13,14,18] that early in the course of such disease the appearance of Bence Jones bodies in the urine may be intermittent and may become constant only late.[1] Aside from these variables, the behavior of the protein depends on many circumstances such as the concentration of the Bence Jones protein, the pH of the urine, the concentration of urinary electrolytes, urea and albumin.

The occurrence of Bence Jones proteinuria has been reported in diseases other than multiple myeloma: metastatic carcinoma, lymphatic leukemia, myelogenous leukemia, senile osteomalacia, fibrocystic disease, multiple fractures of bone, inactive pulmonary tuberculosis, etc.

A rough test for the presence of Bence Jones protein is the sulfosalicylic acid test which is carried out as follows: To 1 cc. of clear urine add three drops of a 20 per cent solution of sulfosalicylic acid. If no cloudiness appears, protein is absent. If a cloud develops, heat the mixture to boiling and then cool. If cloudiness persists on boiling and remains on cooling, albumin and globulin are both present. If cloudiness disappears on boiling and reappears on cooling, either proteose or Bence Jones protein is probably present. If Bence Jones protein and/or albumin and globulin are present, the cloudiness does not completely disappear but becomes less dense on heating. The presence of a positive sulfosalicylic acid test for Bence Jones protein is indication for

the more laborious method of heating the urine specimen in a water bath in which the temperature is slowly raised. Attempts at establishing the existence of Bence Jones bodies in urine sometimes meet with failure because of improper attention to the method of heating the urine. We have obtained best results by heating the urine specimen in a water bath, slowly raising the temperature from 40°C. to 100°C. during a period of fifteen or twenty minutes. This slow method of heating makes it easier to discern the presence of a protein in the urine specimen and at what temperature it precipitates or disappears. A cloudiness appearing at a temperature of 45°C. to 65°C., disappearing on boiling and reappearing on cooling at 65° to 85°C. indicates the presence of Bence Jones protein. If albumin is also present, confusion may result. This may sometimes be avoided by filtration of the urine specimen while boiling, thus removing the coagulated albumin from solution and leaving the Bence Jones protein in the filtrate. Subsequent heating and cooling of the filtrate as noted above may then be carried out and the existence of Bence Jones protein established or disproved.

The term *Bence Jones protein* does not refer to a single chemical entity but to a group of proteins with closely related properties. According to Bayne-Jones and Wilson[22] there are at least three immunologically distinct types of this protein, and Hektoen and Welker[23] have reported two cases in which two of these types were excreted in the urine simultaneously. Moore et al.[24] have found widely different electrophoretic mobilities for urinary Bence Jones protein from different patients. This is in accord with our experience. These authors have confirmed the observation of Svedberg[20] that protein specimens from different patients give sedimentation constants ranging from 2.8 S to 3.7 S. In spite of these variations the generally accepted values for the molecular weight of Bence Jones protein are 35,000 to 37,000.[19,20,24]

Bence Jones protein has been obtained in crystalline form at least fourteen times but, as Magnus-levy[21] has shown, it is frequently very difficult or apparently impossible to crystallize, perhaps because it may be excreted in combination with a pseudoglobulin. Sometimes crystallization is difficult or impossible because of the presence in a single urine of two different varieties of Bence Jones protein. In one case observed by the others, the urine regularly contained large and nearly equal amounts of two proteins migrating during electrophoresis as separate peaks of slightly different mobility. When these proteins were separated from each other in nearly pure form, the solutions of each were found to display in identical manner the well known temperature-solubility relationships of Bence Jones protein. All attempts at crystallization failed.

Plasma Proteins. Elevated total plasma protein (over 8.0 Gm. per cent by modified Howe technic) occurred in 52 per cent of our cases. The highest level was 13.4 Gm. per cent; the lowest 5.0 Gm. per cent. Hyperglobulinemia was present in 67 per cent. It is important to remember that because of a lowered albumin level, the hyperglobulinemia may be present without hyperproteinemia. (Table 1.)

Gutman et al.[25] and Snapper[26] have reported that on the basis of Howe fractionation studies all cases of multiple myeloma in which hyperglobulinemia is present fall into the following four categories listed in order of diminishing frequency: (1) Elevated euglobulin (plus pseudoglobulin 1); (2) elevated pseudoglobulin 1; (3) elevated pseudoglobulin 1 and 11; (4) elevated pseudoglobulin 11. These authors have also studied the globulin distribution in the following diseases associated with hyperglobulinemia: Lymphogranuloma venereum, sarcoid, cirrhosis, kala-azar, disseminated lupus, subacute bacterial endocarditis, leprosy, tubercular lymphadenitis, rheumatoid arthritis, leukemia, chronic nephritis and a few miscellaneous infections. All of these cases were found to belong in group 1. It therefore follows that whenever hyperglobulinemia of groups 2, 3 or 4 is present, the disease is probably multiple myeloma. Fractionation

is of no diagnostic aid when the findings place it in the first category.

Gutman et al.[25] have pointed out that in some cases of multiple myeloma the conventional Howe fractionation technic may yield albumin values that are grossly too high, but that in these instances more protein may precipitate with the globulin fraction if a longer time is allowed before filtration.

Since our belief is that electrophoresis is the method of choice, we have not fractionated the globulins by the Howe method in our cases.

TABLE I

LABORATORY FINDINGS IN SIXTY-THREE CASES OF PLASMA CELL TUMORS

	Normal	Elevated	Depressed	Not Done	Highest Values	Lowest Values	Average
	No. of Cases						
White blood count	45	10	7	1	51,200 per cu. mm.	3,000 per cu. mm.	8,075 per cu. mm.
Red blood count	9	..	51	3	6.1 million per cu. mm.	1.46 million per cu. mm.	3.09 million per cu. mm.
Hemoglobin	9	..	54	..	15.5 Gm. %	5.1 Gm. %	9.8 Gm. %
Serum calcium	30	11	4	18	19.9 mg. %	6.2 mg. %	11.0 mg. %
Serum phosphorus	32	10	3	18	10.5 mg. %	2.1 mg. %	4.4 mg. %
Total plasma proteins	22	27	3	11	13.4 Gm. %	5.0 Gm. %	8.4 Gm. %
Serum albumin	8	0	43	12	5.6 Gm. %	1.0 Gm. %	3.5 Gm. %
Serum globulin	16	34	1	12	11.4 Gm. %	1.0 Gm. %	5.0 Gm. %
Non-protein nitrogen	31	26	..	6	285 mg. %	.....	62 mg. %

ELECTROPHORETIC STUDIES

The value of electrophoresis in the diagnosis of multiple myeloma was first revealed in 1939 by Longsworth, Shedlovsky and MacInnes[8] who found rather characteristic abnormalities in two cases and normal patterns in one case. In 1940 Kekwick[27] published the results of combined electrophoretic and ultracentrifugal studies in five cases. The most extensive studies reported have been by Gutman et al.[25] and Moore et al.[24] The latter paper deals at length with the problem of Bence Jones proteinemia and the relation of Bence Jones protein to the abnormal peaks in the electrophoretic patterns. In these two papers there are reported twelve new cases studied by electrophoresis. In four of these cases there was an abnormally large γ peak, which in two instances was associated with a small peak referred to as an M component migrating with the mobility of fibrinogen. Three cases showed a large β peak, two a large M peak and one a small M peak. In two cases the patterns were described as normal.

On the other hand, we have encountered no normal patterns in thirty-three consecutive cases, the first twenty-nine of which are described in this paper. We ascribe the discrepancy in these findings to two factors: (1) Our use of the 2:1 dilution of plasma by sodium-barbital buffer as advocated by Longsworth in 1942[28] and (2) the use of the tall form of the Tiselius cell with a wider spread of the electrophoretic peaks. Under these conditions small abnormalities are revealed which would otherwise not be apparent. These abnormalities, while small, are reproducible and significant.

Methods of Electrophoresis. Plasma was used in all cases although occasionally additional patterns were obtained from serum.

In order to demonstrate small irregularities, the high dilutions of plasma frequently recommended were avoided. The plasma was diluted with an equal volume of veronal

TABLE II

ELECTROPHORETIC FINDINGS IN THIRTY CASES OF PLASMA CELL TUMOR

Case No.	Interval after First Sample	Urinary Bence Jones Protein	Mobility of Abnormal Peak	Protein Concentrations in Gm. Per Cent								Remarks
				Abnormal Peak	Total	Albumin	Alpha$_1$	Alpha$_2$	Beta	Phi*	Gamma	
1	.....	0	Less than gamma	2.4+	8.1+	3.1	0.2	0.8	0.8	0.5	0.2	
1	2 mo.	0	Less than gamma	2.4+	7.4+	2.5	0.3	0.8	0.7	0.4	0.3	After stilbamidine therapy
2	.....	0	Less than gamma	2.3+	7.9+	3.0	0.4	0.8	0.9	0.3	0.3	
3	.....	0	Less than gamma	5.5+	11.8+	3.1	0.5	1.3	0.6	0.8*	0.0?	* Value from ascending pattern is 0.30
4	.....	0	Less than gamma	2.4+	8.0+	3.2	0.4	0.6	0.6	0.8	0.0?	
4	1 mo.	0	Less than gamma	2.4+	7.5+	2.6	0.5	0.7	0.8	0.4	0.0?	
5	.....	0	Less than gamma	2.9+	8.4+	3.2	0.3	0.7	0.7	0.4	0.1	
6	.....	+	Less than gamma	2.6+	8.6+	2.9	0.5	1.0	0.7	0.4	0.4	
7	.....	+	Equal to gamma	2.3	8.0	3.1	0.4	0.8	0.6	0.7*	2.3	* Value from ascending pattern is 0.47
8	.....	0	Equal to gamma	2.3	7.8	2.2	0.6	0.9	1.1	0.8	2.3	
9	.....	0	Equal to gamma	5.9	9.5	1.7	0.3	0.6	0.5	0.5	5.9	During lobar pneumonia
9	3 wk.	0	Equal to gamma	5.3	8.9	1.6	0.3	0.6	0.5	0.5	5.3	After pneumonia
9	1 yr.	0	Equal to gamma	4.1	8.5	2.2	0.3	0.6	0.6	0.6	4.1	
10	.....	0	Equal to gamma	3.0+	9.9+	2.2	0.7	1.2	1.0	1.7*	3.0	* Value from ascending pattern is 0.87
11	.....	0	Equal to gamma	6.2	11.1	3.3	0.3	0.5	0.4	0.4	6.2	
12	.....	+	Between phi and gamma	2.9+	5.2+	1.4	0.1	0.3	0.5	2.9+		
13	.....	+	Between phi and gamma	7.2	10.4+	1.9	0.3	0.6	0.4	7.2+		
14	.....	0	Equal to phi	2.4+	6.8+	2.5	0.5	0.8	0.5	2.4+	0.2	
15	.....	0	Equal to phi	4.1	8.9	3.0	0.4	0.7	0.6	4.1		
16	.....	0	Equal to phi	5.7	8.7	1.7	0.4	0.7	5.7	.....	0.1	
17	.....	0	Between beta and phi	6.5+	9.6+	2.1	0.3	0.6	6.5+	.....	0.1	
18	.....	+	Equal to beta	4.8+	10.2+	3.6	0.6	1.0	4.8+	.....	0.3	
19	.....	0	Equal to beta	7.9+	11.8+	2.1	0.4	0.6	7.9+	0.6	0.2	
20	.....	+	Equal to beta	6.1	9.0	2.3	0.3	6.1	.....	0.3	0.1	
21	.....	+	Equal to beta	6.3+	8.9+	1.8	0.5	6.3	.....	0.2	0.2	
22	.....	+	Between phi and gamma	?	7.0	3.2	0.5	0.8	0.7	1.8		
23	.....	+	Sharp gamma	.....	6.4	3.5	0.5	0.8	0.7	0.5	0.4	
24	.....	+	Sharp gamma	.....	8.1	3.8	0.6	1.2	0.9	0.6	0.9	
25	.....	+	Sharp gamma	.....	6.3	3.2	0.5	1.0	0.8	0.3	0.4	
26	.....	+	Less than gamma	0.1	5.9	3.2	0.5	0.9	0.6	0.4	0.2	
27	.....	+	Bulge on phi	.....	6.4	4.2	0.2	0.7	0.7	0.5	0.1	Plasma cell leukemia
28	.....	?	Bump on gamma	.....	6.1	3.0	0.4	1.1	0.8	0.4	0.4	Hepatic cirrhosis
28	3 mo.	0	Bump on gamma	.....	6.8	3.5	0.5	1.2	0.9	0.3	0.5	Bump slightly larger
28	11 mo.	0	Bump on gamma	.....	7.2	4.0	0.3	1.0	0.8	0.6	0.5	Bump still larger
29	.....	+	Bump on gamma	.....	6.5	2.1	0.9	1.2	1.1	0.8	0.4	2 days before death
30	.....	0		.....	7.4	2.8	0.8	1.1	1.0	1.0	0.6	1 day postoperatively solitary myeloma of antrum
30	7 mo.	0		.....	6.9	3.2	0.4	0.8	0.9	0.7	0.8	
Normal average (20 plasmas)	.....	..		.....	6.9	4.1	0.4	0.6	0.8	0.3	0.7	

* Represents fibrinogen plus a small amount of gamma globulin.

buffer of pH 8.5 and ionic strength 0.1. This diluted plasma was dialyzed in a cellophane sac against 2 L. of the veronal buffer. Mechanical rocking in the refrigerator permitted satisfactory equilibration in sixteen hours.

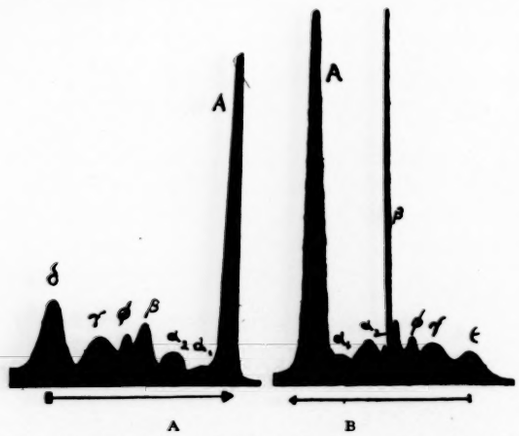


FIG. 3. Ascending (left) and descending (right) patterns of normal human plasma.

Electrophoresis was carried out in the tall form of the standard 11 ml. Tiselius cell at a field strength of about 6.8 volts per cm. at a water bath temperature of 1°C. The current was passed for at least three hours. The patterns were photographed by the scanning method of Longsworth[29] and the areas of the peaks were obtained from photographic enlargements by the use of a planimeter. If the Tiselius cell with a double center section is employed, the spread of the peaks is too small to reveal some important details. A more complete account of the methods may be found in a previous paper.[30]

Because of the 2:1 plasma dilution routinely employed, many of the large abnormal peaks extended beyond the range of the photographic plate. This made it impossible to measure the area of such a peak although in some instances its height was determined by measuring the distance in the plane of the schlieren diaphragm between the undeviated slit image and the most deviated image and multiplying by three. We preferred to sacrifice an accurate determination of the area of large abnormal peaks in order to stabilize small peaks by a higher density gradient and to increase slight irregularities. Higher dilutions give patterns which more accurately reflect the concentrations of the plasma constituents but this theoretic gain is offset by a practical loss.

Results of Electrophoresis. In Table II and in descriptions of some of the patterns we frequently refer to "abnormal" peaks. This is unfortunately an ambiguous term. An "abnormal" peak may indicate either the presence of an abnormal concentration of a normal plasma constituent or the presence of a protein not found in normal plasma.

The results of these electrophoretic studies may best be divided into four groups according to the type of pattern present: (1) major abnormal patterns showing tall, narrow peaks, twenty-one cases; (2) minor abnormal patterns showing slight irregularities, eight cases; (3) normal patterns from one case of solitary myeloma; (4) abnormal patterns which might be confused with multiple myeloma, five cases. For comparison with these and subsequent patterns, normal patterns are shown in Figure 3.

1. The first twenty-one cases of plasma cell tumors are tabulated in the order of increasing mobility of the abnormal peak (Table II) which varied from slower than gamma to as fast as beta.* The patterns of this group all showed narrow, tall peaks, usually so tall that they extended beyond the edge of the photographic plates. In this group of twenty-one cases the mobilities of the abnormal peaks showed the following distributions: less than gamma in six cases; equal to gamma in five cases; between gamma and fibrinogen in two cases; equal to fibrinogen.in three cases; between fibrinogen and beta in one; equal to beta in four. Figure 4 shows the patterns from Case 17 illustrating an abnormal peak migrating between fibrinogen and beta. Space does not permit showing patterns illustrating all

* An article recently published reports two cases with large abnormal peaks migrating with the mobility of alpha$_2$ globulin. WUHRMANN, F., WUNDERLY, C. and WIEDEMANN, E., Ueber das Alpha-Globulin-Plasmocytom. *Schweiz. med. Wchnschr.*, 78: 180, 1948.

the various mobilities which have been frequently reported for these characteristic tall, narrow peaks. A single example of a frequently reported type of pattern is shown in Figure 4.

Figure 5 from Case 6 shows a peak migrating more slowly than gamma globulin (not previously reported to our knowledge). This example is chosen because it shows a curious phenomenon. The current was passed for thirty minutes longer than the usual three hours. During the last twenty minutes the gamma peak in the ascending pattern split into two components. The low gamma concentration is noteworthy.

Figure 6 shows the patterns of Case 8. They are somewhat atypical in that abnormal gamma peak is of intermediate height.

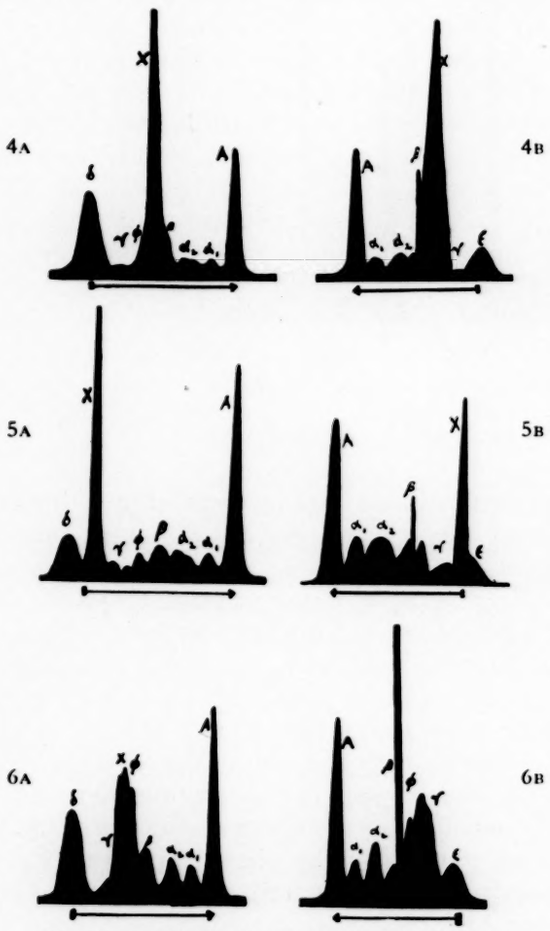


FIG. 4. A and B, major abnormality (Case XVII, multiple myeloma) migrating between fibrinogen and beta globulin.
FIG. 5. A and B, major abnormality (Case VI, multiple myeloma) showing a peak migrating slower than gamma globulin.
FIG. 6. A and B, major abnormality (Case VIII, multiple myeloma); abnormal gamma peak is of intermediate height.

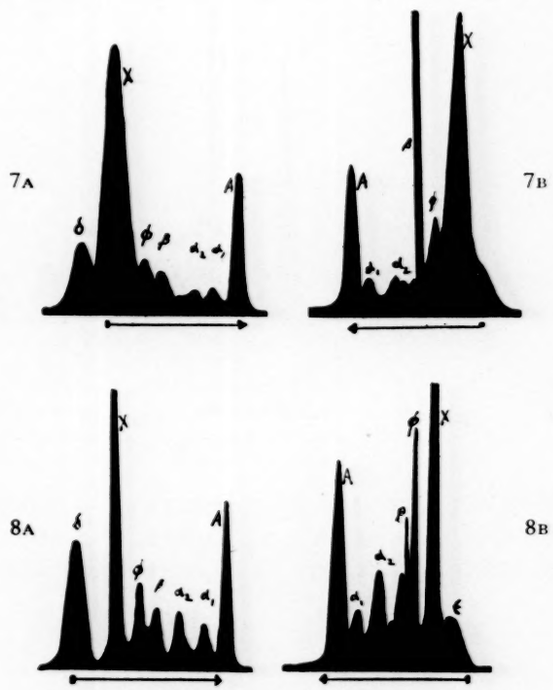


FIG. 7. A and B, major abnormality (Case IX, multiple myeloma and lobar pneumonia); note broad gamma peak.
FIG. 8. A and B, major abnormality (Case X, multiple myeloma given massive roentgen treatment); note increase in all globulins and the difference in height of the fibrinogen peak in the ascending and descending patterns.

Figure 7 shows the patterns from Case 9 taken during coincident lobar pneumonia. This is an atypical and ambiguous pattern. The unusual feature is the width of the gamma peak in relation to its height. Subsequent patterns after recovery from pneumonia showed some changes in peak areas but the gamma remained broad for its height. It is possible that chronic hepatitis was present. These patterns are practically identical with those seen in one fatal case of subacute hepatitis. The patterns are so similar that it is unnecessary to show them both. We have patterns from fifty-nine other cases of hepatic disease, but these are

the only pair which might be confused with those seen in multiple myeloma. The failure of alpha$_1$, alpha$_2$ and fibrinogen to rise in Case 9 during lobar pneumonia is worthy of note.

Figure 8 shows the patterns of Case 10; they are very unusual. While the abnormal gamma peak is tall and sharp, the other globulin peaks are all increased. The fibrinogen peak in the descending pattern is twice as large as in the ascending. (A similar asymmetry is found in Cases 3 and 7.) It is interesting to note that this unique pattern is associated with an unusual case history. The patient lived over five years after his disease was recognized and during these years received roentgen radiation totaling 30,000r.

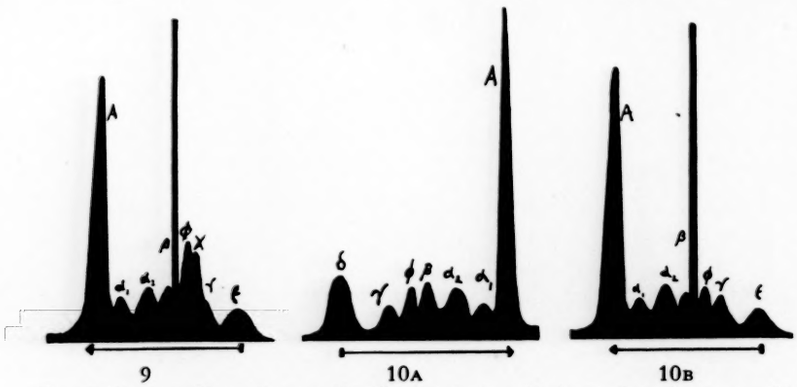


FIG. 9. Intermediate abnormality (Case XXIII, multiple myeloma); note small peak migrating close to gamma globulin.
FIG. 10. A and B, minor abnormality (Case XXII, multiple myeloma); note relatively sharp small gamma peak.

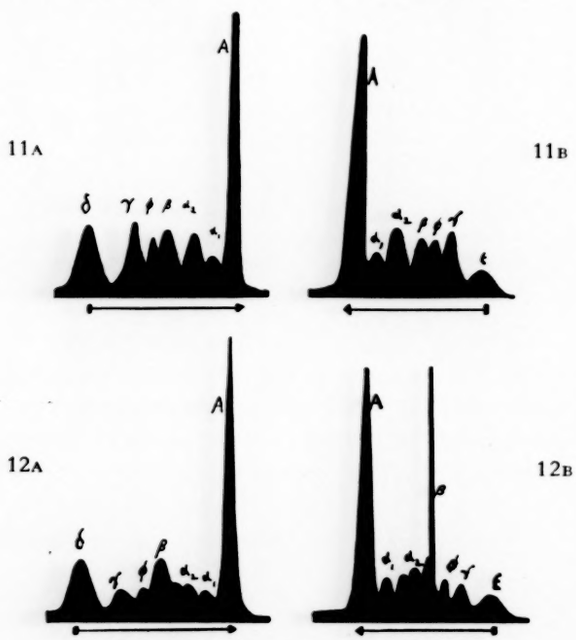


FIG. 11. A and B, minor abnormality (Case XXIV, multiple myeloma); note sharp gamma peak and moderate hyperglobulinemia.
FIG. 12. A and B, minor abnormality (Case XXV, multiple myeloma); note sharp gamma peak particularly in the descending pattern.

2. The eight patterns from Cases 22 to 29 are of special interest because they are of a type not hitherto reported in multiple myeloma. These abnormalities would probably pass unnoticed if the plasma were diluted four to one, or if the Tiselius cell with the double center section were employed. (The small abnormalities are much more obvious in the photographic enlargements than in the reduced figures shown here.)

Case 22 shows a small abnormal peak. (Fig. 9.) This pattern is intermediate in type between the first twenty-one and the following seven.

The patterns of Cases 23, 24 and 25 are shown in Figures 10, 11 and 12, respectively. In these three cases the gamma peaks, while not large, are sharp instead of being rounded as in the normal. In Case 24 the other globulin peaks are sufficiently elevated to produce a moderate hyperglobulinemia. In our experience this type of peak was encountered in only one disease other than myeloma. This exception was a case of

adenocarcinoma of the stomach with metastases to the esophagus, liver and regional lymph nodes. The patterns from this case are shown in Figure 13. It will be seen that in the ascending pattern the gamma peak is abnormally sharp and is more irregular than in the three cases of multiple myeloma.

In Case 26 (Fig. 14) the descending pattern shows a small bump migrating more slowly than gamma. We have seen no other pattern like this.

Case 27 (Fig. 15) is a "plasma cell leukemia." The gamma is very low. In the ascending pattern an abnormal bulge is seen on the gamma side of the fibrinogen peak. The mobility of this bulge is the same as that of the pure Bence Jones protein peak in the patient's urine.

There are two striking features in the electrophoretic pattern of Case 28 (a case of hepatic cirrhosis and multiple myeloma). The patterns shown in Figure 16 were obtained from a plasma sample taken eleven months after the initial sample. During this time the albumin concentration rose to normal levels (a low albumin is the most common single finding in malignant disease) and the small irregularity on the leading edge of the gamma peak became more pronounced. We have encountered a small irregularity in this location (ascending pattern) only in malignant disease (16 per cent of 275 cases), acute infections such as pneumonia and pneumococcal meningitis, immediately following surgical operation and in six cases of multiple myeloma.

Figure 17 shows the ascending pattern from Case 29. There is a similar irregularity on the leading edge of the gamma peak. All the globulin peaks except gamma are increased. This patient was admitted to the hospital in uremia and the blood sample was taken two days before death.

3. Case 30 is one of solitary myeloma of the antrum. The first patterns show abnormal elevations of all the globulins except gamma. These abnormalities were probably the result of surgical exploration of the antrum which was done the day before the blood sample was taken. During this operation a massive hemorrhage occurred. The patterns from a blood sample taken seven months later were normal except for a rather low albumin and an elevated fibrinogen. These abnormalities were probably due to the infection associated

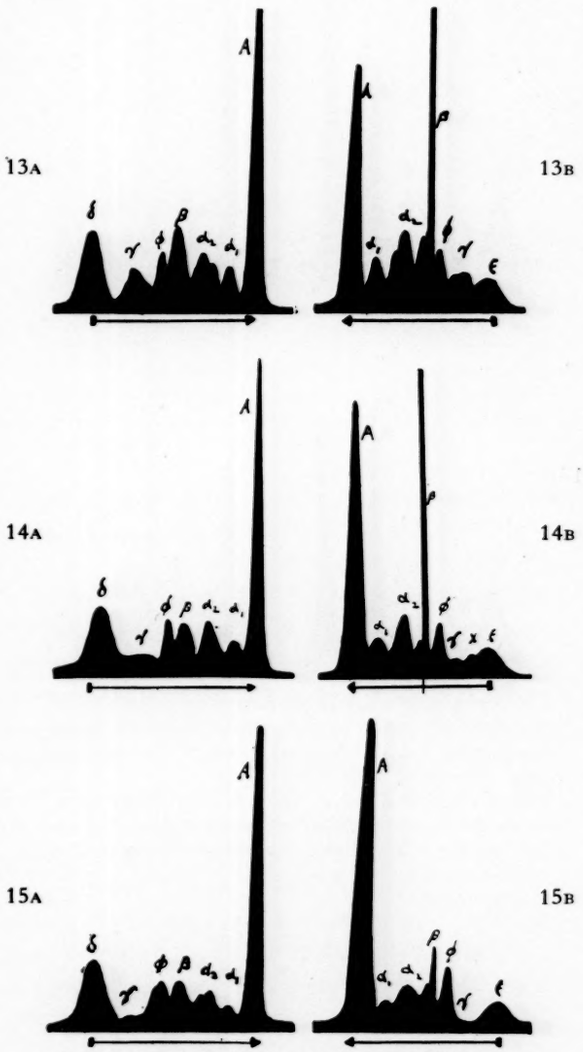
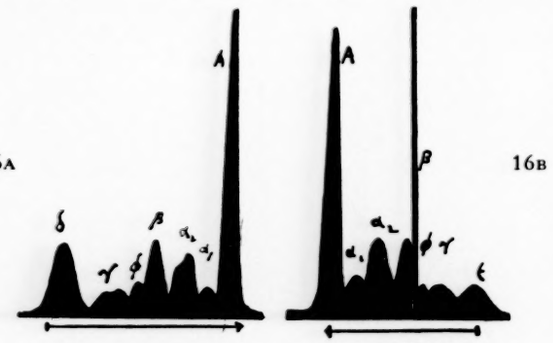


FIG. 13. A and B, pattern from a case of adenocarcinoma of the stomach with metastases to the esophagus, liver and regional lymph nodes; note similarity to the patterns in Figures 10, 11 and 12.

FIG. 14. A and B, minor abnormality (Case XXVI, multiple myeloma); note small bump migrating slower than gamma globulin in the descending pattern.

FIG. 15. A and B, minor abnormality (Case XXVII, "plasma cell leukemia"); note low gamma globulin and the abnormal bulge on the gamma side of the fibrinogen peak in the ascending pattern.

with a persistent draining sinus tract at the site of operation. Since widespread disease was probably absent as indicated by bone marrow studies, it is not surprising that these patterns showed none of the abnormalities which are suggestive of multiple myeloma.



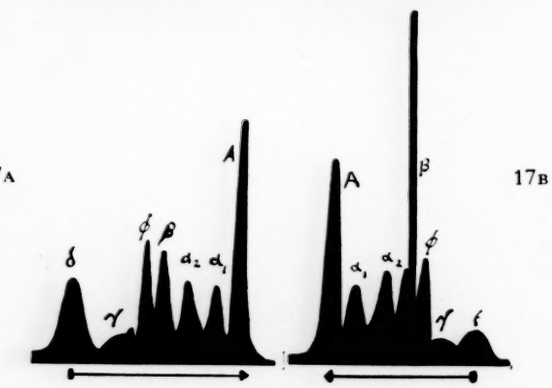


FIG. 16. A and B, minor abnormality (Case XXVIII, multiple myeloma and cirrhosis); note the small irregularity on the leading edge of the gamma peak (ascending pattern).
FIG. 17. A and B, minor abnormality (Case XXIX, multiple myeloma); note the small irregularity on the leading edge of the gamma peak (ascending pattern) and the elevation of all the globulin peaks except gamma.

In the first twenty-one cases (except Case 18) the plasma albumin level was below normal and often very low. The average value for this group was 2.5 Gm. per cent. In the entire series of sixty-three cases the albumin concentration as determined by the Howe method was below normal in 86 per cent.

Special attention should be drawn to the fact that the concentration of gamma globulin was usually very low unless the abnormal peak migrated with a mobility equal to or close to that of gamma globulin in which event we have no way of measuring the concentration of normal gamma globulin. It may be that a low concentration of normal gamma globulin is a constant and important feature of multiple myeloma.

4. We have five instances in which patterns showed abnormalities which might falsely suggest multiple myeloma. (Figs. 6, 13, 18, 19 and 20.) The patterns in Figure 6 are almost identical with those seen in one case of hepatitis and are therefore not reproduced. Figure 13 is from a case of gastric malignancy. Figure 18 shows the ascending pattern from the *serum* of a case of hepatic cirrhosis. There is evidently an abnormal peak migrating with the mobility of fibrinogen. It is not well separated from the large, broad gamma peak so commonly found in cirrhosis. This peak is probably not due to residual fibrinogen since the

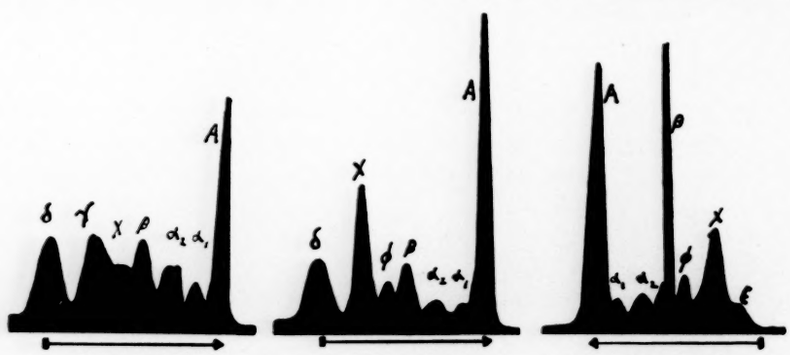


FIG. 18. Ascending pattern from the serum of a case of hepatic cirrhosis; note abnormal peak migrating with the mobility of fibrinogen.
FIG. 19. A and B, patterns from a case of degenerative arthritis; note abnormal gamma peak.

addition of thrombin failed to remove it. A similar pattern is reported by Stern and Reiner[31] in a case of cirrhosis. Even though this pattern shows an abnormal peak, we do not believe it could be confused with a pattern of multiple myeloma. Figure 19 shows the patterns from a patient who presented old degenerative arthritic changes in one humerus and both femoral heads. The blood serum showed an anomaly in that the cephalin flocculation reaction was one plus while the thymol turbidity reading was 169 units. The sternal marrow was normal. It is of course possible that this is an early case of myeloma. A second set of patterns taken six months later showed no change. Figure 20 shows the pattern from a patient who had wide spread bone and pulmonary metastases from a carcinoma of unknown primary site. This patient died in another hospital and no autopsy was performed. It seems unlikely, however, that he had multiple myeloma although we have recently seen an almost identical pattern in a case which was found at autopsy to have this disease. Increased experience may or may not permit the differentiation of such patterns.

Discussion of Electrophoretic Results. Ultracentrifugal and diffusion studies[27,32,33,34] have shown that the large abnormal peaks in the patterns of multiple myeloma are usually due to proteins of high molecular weight (160,000–200,000) but may occasionally be due to low molecular weight proteins, probably Bence Jones proteins.

Moore et al.[24] studied the sera of seven cases of multiple myeloma by the Howe fractionation method, electrophoresis and the ultracentrifuge. In two of these cases Bence Jones protein was demonstrated in the plasma by immunologic methods. Both of these cases were excreting this protein in the urine. In another case without Bence Jones proteinuria the presence of this protein in the plasma was indicated by ultracentrifugal studies. The many interesting findings reported by these authors cannot be reviewed in detail. One of their conclusions is that in "many (probably the majority of) cases of multiple meyloma with marked hyperglobulinemia" only a very small proportion of the excess of globulins is Bence Jones protein.

Sedimentation diagrams of the high molecular weight proteins are often similar

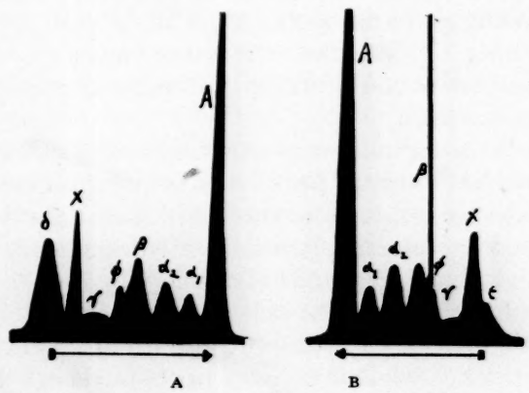


FIG. 20. A and B, patterns from a case of widespread osseous metastases from a carcinoma of unknown primary site.

to those of normal gamma globulin but are sometimes very different, corresponding to no known constituent of normal plasma. It is well known that proteins may have similar electrophoretic mobilities and sedimentation characteristics and yet be different chemically. This fact usually makes it impossible to determine by these two means alone whether a given protein is abnormal or not. The large peaks in the first six cases in Table II probably represent abnormal proteins since there is no detectable protein in normal plasma which migrates more slowly than gamma globulin. It is curious that a peak migrating more slowly than gamma has not to our knowledge been previously reported in multiple myeloma. The probable explanation lies in the fact that most of the earlier electrophoretic studies of multiple myeloma were made with buffers in which the normal gamma peak did not migrate away from the boundary anomaly.

With the exception of Case 9, all of the abnormally large peaks with the mobility of gamma globulin were too narrow to be confused with the large gamma peaks produced by diseases other than myeloma.

Such diseases include hepatitis (acute and chronic), disseminated lupus, lymphogranuloma venereum, kala-azar, tuberculosis, amyloidosis, scleroderma and monocytic leukemia. The narrowness of the myeloma peaks probably indicates that the proteins are more homogeneous than those comprising gamma globulin. This is not surprising in view of the large number of antibodies contained in the gamma globulin fraction.

In order to reveal this important difference in width of peaks it is essential to employ the tall form of the Tiselius cell and to continue electrophoresis until the albumin peak has migrated about 5 cm. in the cathode limb of the cell.

Wintrobe[35] has commented on the higher incidence of Bence Jones proteinuria when hyperglobulinemia is absent. We have found a similar difference in our two main groups of cases. In the first twenty-one cases, all of which showed large abnormal peaks, urinary Bence Jones protein was detected only seven times, an incidence of 33.3 per cent. In the group containing the next eight cases, all of which showed small abnormalities, urinary Bence Jones protein was found in seven and may have been present on one occasion in the eighth. It is plausible to suggest that at least some of the small abnormalities were due to Bence Jones protein in the plasma. This is especially likely in Cases 22, 23, 24, 25 and 27. In several of these cases the urine showed no protein other than Bence Jones protein and electrophoretic patterns of the urine showed a single peak of the same mobility as the small abnormal peaks in the plasma. If a Bence Jones protein were present in the plasma uncombined with other protein, it should appear in the urine because of its small molecular size. Moore et al.[24] have suggested that complex formation with a high molecular weight protein may prevent the escape of Bence Jones protein through the kidney. This hypothesis is attractive to us. The lack of symmetry between the ascending and descending patterns in Cases 3, 7 and 10 suggests such complex formation. This hypothesis would partially explain the high incidence of Bence Jones proteinuria in the eight cases, 22 through 29. These cases did not have any large amount of abnormal, high molecular weight protein to bind the Bence Jones protein.

The problem of the origin of Bence Jones protein and the high molecular weight proteins is totally obscure. There is no direct evidence that Bence Jones protein is produced by plasma cells. In our experience whenever this protein is found in the urine, plasma cells are found in excess numbers in the bone marrow or other tissues. Magnus-Levy believed that the large amount of protein occasionally produced (30 to 70 Gm. in twenty-four hours) could not be produced by the relatively small mass of tumor tissue. However, this objection has lost its force since it is now known that the disease is a diffuse one in which bone marrow is widely involved. It is also well to point out that the volume of the bone marrow is surprisingly large; as reported by Fairman and Whipple,[36] it is equal to two-thirds the volume of the liver in dogs.

In our series of cases we have found no apparent correlation between the number and morphology of plasma cells in the sternal marrow and the presence or absence of hyperglobulinemia, or the electrophoretic mobility of the abnormal peaks.

Increased Plasma Cells in Sternal Marrow (86 per cent). In few other hematologic disorders is the sternal puncture of more help in making a diagnosis than in multiple myeloma. As a rule, by the time signs and symptoms are present the disease is already far advanced and the sternum infiltrated with plasma cells. Bone marrow biopsy and/or puncture of the sternum were carried out in thirty-six cases in this series. In only five cases were the results of examination of material taken from the sternum equivocal. These five cases were later proved to be multiple myeloma by examination of material taken from other bony sites or at postmortem examination. The average per cent of plasma cells in the

sternal marrow in thirty-one cases of myeloma was 36.2 per cent. The greatest per cent of cells was 83.6 per cent, the least 6.7 per cent. These cells appear to stem from one common line—the plasma cell line (no cases of myeloma have been seen by us in which the plasma cell or its precursors was not the invading cell). It is true that these cells present a somewhat variable morphologic picture but it seems plausible that this difference in appearance may be due to differences in age. In some cases of multiple myeloma the most frequent cell seen (Wright's stain) is a large cell 20 to 30 mμ in diameter with a dark blue, somewhat scroll-like cytoplasm which contains no granules. The nucleus is round or oval and may occupy three-fourths to four-fifths of the entire cell. Its chromatin is evenly distributed throughout the nucleoplasm. There may be as many as three or four nucleoli contained within the nucleus. Mitotic figures are common. There are all gradations from this "malignant" type of cell down to the "typical" plasma cell. This latter cell measures 7 to 12 mμ in diameter. The cytoplasm is dark blue and gathered in homogeneous · knots. The nucleus is placed eccentrically and fills less than one-half the cell volume; its chromatin is condensed, many times appearing pyknotic. The most characteristic feature is the appearance of the cytoplasm which, if once clearly recognized, is almost unmistakable. In fact in certain of our bone marrow preparations fragments of the cytoplasm were often seen which had evidently been broken from a myeloma or plasma cell, but which remained clearly recognizable. The presence of these cells in greater numbers than 2 to 3 per cent is considered to be abnormal, and when present in large numbers, to be diagnostic of multiple myeloma. It is the preference of this clinic to obtain both sternal aspiration and bone marrow biopsy material so that the hematologist and pathologist may collaborate in the diagnosis. It should be remembered that certain cases of multiple myeloma show a patchy plasma cell infiltration of the bone marrow and that it is possible in these cases to be misled by the results of sternal aspiration. A low percentage of plasma cells in material aspirated from the bone marrow does not necessarily rule out the diagnosis of multiple myeloma.

Anemia (86 per cent). The red blood coun was depressed in 81 per cent of the cases. The average count was 3.09 million per cu. mm., the extremes being 1.46 and 6.1 million per cu. mm. It should be noted, however, that the anemia, although a fairly constant finding, was seldom extreme as, for example, in pernicious anemia. The anemia was usually normocytic and normochromic in type although in 14 per cent of the cases there was a macrocytosis. Only infrequently was the macrocytosis so pronounced that the diagnosis was confused with pernicious anemia.

Just as with the red blood count, the hemoglobin values were commonly depressed. In fifty-four cases (86 per cent) the hemoglobin determinations fell below 13.0 Gm. per cent and in only nine cases was the hemoglobin found to be within normal limits. The highest value recorded was 15.5 Gm. per cent; the lowest 5.1 Gm. per cent. The average hemoglobin was 9.8 Gm. per cent. It can be said that the occurrence of anemia at some stage in the course of this disease is very frequent and that the presence of the disease in the absence of anemia is distinctly unusual. The presence of unexplained anemia, particularly in the older age groups, is of great importance. Many more diagnoses of this condition will be made if more careful studies of unexplained anemias are carried out.

X-ray Changes (86 per cent). The typical findings upon x-ray examination in cases of multiple myeloma have been adequately described elsewhere. However, in the study of this group of cases certain observations have been made. The commonest (although far from diagnostic) x-ray change is one of widespread osteoporosis involving the entire skeleton. We have been struck with the uniformity of occurrence of this change and have seen cases in which this was the only

roentgenographic finding. Secondly, the occurrence of small "flea bitten" areas of rarefaction without evidence of surrounding new bone formation is not infrequent. These areas are seen in the long bones, pelvis, vertebrae, ribs and calvarium. They resemble somewhat the x-ray changes seen in leukemia. Thirdly, the most characteristic change is the appearance of the typical "punched out" area with its sharp margination without evidence of surrounding osteoblastic change. When these changes are widespread in the skull, vertebrae, ribs, etc., they are highly suggestive of multiple myeloma and in at least seven instances in this series the correct diagnosis was first suggested by the roentgenologist. Fourthly, there are a certain few cases of multiple myeloma which never exhibit x-ray changes of any type. Two such cases have been seen by us.

From the roentgenographic standpoint the commonest bones involved in order of diminishing frequency were: vertebrae, skull, ribs, pelvis, clavicle, femur, humerus, scapula, fibula, mandible and radius. Any one, or, as is sometimes seen, practically all the bones of the skeleton may be involved.

Rouleaux Formation (60 per cent). Hewson (1777),[37] De Senac (1783)[38] and Home (1818)[39] made note of the phenomenon of rouleaux formation during the process of blood coagulation. In 1851 Wharton Jones[40] noted the increased tendency to rouleaux formation in persons "labouring under acute rheumatism or inflammation." This fact has been confirmed by many investigators since 1851 but it was not until 1932 that Reimann[41] drew attention to its occurrence in a case of multiple myeloma. The altered plasma proteins so common in multiple myeloma exert a profound effect on many laboratory procedures. Because of excessive rouleaux formation, red blood counts become difficult to do accurately, blood typing may be confusing, the sedimentation rate is extremely rapid and smears of the peripheral blood appear technically imperfect. As Fåhraeus[42] has stated, the phenomenon of excessive rouleaux formation is probably due to the changes in electric charge which result primarily from the alteration of the albumin-globulin ratio. The exact mechanism of increased rouleaux formation, however, remains obscure. In the last ten cases of myeloma which we have seen, six have shown increased rouleaux formation in the peripheral blood smear. Even in thin areas of the blood smear the red cells are seen to be piled one upon another. Excessive rouleaux formation occurs in other disorders associated with hyperproteinemia and is not distinctive of multiple myeloma. Besides this increased tendency to rouleaux formation there may be a peculiar bright blue coloration of the peripheral blood smear (Wright's stain). This phenomenon has been observed by others[10] and has been attributed to the elevated plasma proteins. We should like to emphasize the importance of these observations which are sometimes of help in the diagnosis of multiple myeloma.

Renal Insufficiency (57 per cent). Urinary function was depressed in thirty-two of fifty-six cases in which phenolsulfonphthalein excretion and urea clearance tests were done. In only one case of Bence Jones proteinuria were these two tests found to be normal. However, this case was later studied more carefully* and by determination of renal blood flow it was found that at least 50 per cent of the renal units were nonfunctional. Various theories as to how Bence Jones proteinuria interferes with renal function have been postulated. Some authorities believe that there is a "toxic nephritis caused by elaboration of Bence Jones protein." Others have postulated that glomerular damage results from filtration of Bence Jones bodies. Still others have said that damage results from the ischemia caused by large amounts of abnormal protein circulating in the glomerular tuft. Actual tubular obstruction by protein casts associated with degeneration of the renal unit has been considered to be of primary importance. There are many questions to be settled before the true pathogenesis of

* Determinations by Dr. Christine Waterhouse, University of Rochester School of Medicine, Rochester, N. Y.

the renal insufficiency is elucidated. It is interesting that despite the so-called "nephritis" in this condition hypertension is seldom seen (13 per cent). Since Bence Jones proteins are small (35,000–40,000 molecular weight)* and since other proteins which are much larger pass through the glomeruli perhaps without doing permanent damage it seems unlikely that the mechanical filtration of this substance alone can be responsible for the renal damage. Blackman[43] suspects that as the disease progresses and the quantity of urinary Bence Jones protein increases actual tubular obstruction occurs in a certain number of cases and renal failure develops. The true pathogenesis of renal insufficiency in this condition remains a mystery but it is our opinion that once Bence Jones protein is detected in the urine the development of renal insufficiency has begun. As the disease progresses the phenolsulfonphthalein and urea clearance tests gradually become diminished and finally azotemia develops (the blood non-protein nitrogen was elevated in twenty-six of fifty-seven cases in which determinations were made; 46 per cent). Uremia was the mode of exitus in twelve (43 per cent) of twenty-eight cases in which the terminal condition was clear.

Calcium and Phosphorus Metabolism. The serum calcium and phosphorus in cases of multiple myeloma may be altered. In our laboratory the upper limit of the normal serum calcium level is 11 mg. per cent. Levels higher than this were encountered in twenty-four of forty-five cases (53.3 per cent). Levels of 13 mg. per cent or higher were found in seven of forty-five cases (15.6 per cent). The serum calcium was found to be depressed in four cases and normal in thirty. The average value was 11.0 mg. per cent. Phosphorus values were elevated (greater than 5 mg. per cent) in cases in which renal failure had developed (ten cases). The alkaline phosphatase activity (Bodansky) was greater than 4.0 Bodansky units in ten cases (48 per cent) of a total of twenty-one cases in which the determination was made. The highest activity was found to be 26.5 Bodansky units and the lowest 1.7 Bodansky units. The average value was 5.2 Bodansky units. The acid phosphatase values (King-Armstrong) in twenty-one cases were all within normal limits. It can be seen from these figures that the following values are usually found in cases of multiple myeloma: (1) normal or elevated serum calcium; (2) normal serum phosphorus (unless renal impairment supervenes in which case the phosphorus level increases); (3) normal acid phosphatase; (4) normal to slightly elevated alkaline phosphatase. The frequent occurrence of the above findings is of distinct aid in the differential diagnosis of hyperparathyroidism, Paget's disease, metastatic carcinoma to bone and multiple myeloma. (Table III.)

The authors do not wish to convey the impression that the determination of serum calcium, inorganic phosphorus and phosphatase activity are diagnostic in cases of multiple myeloma, but rather that these determinations either lend support to or

TABLE III*

SERUM CALCIUM PHOSPHORUS AND PHOSPHATASES IN VARIOUS BONE DISEASES

Diseases	Calcium	Phosphorus	Acid Phosphatase	Alkaline Phosphatase
Hyperparathyroidism	Elevated	Depressed	Normal	Elevated
Paget's disease	Normal	Normal	Normal	Elevated
Metastatic carcinoma to bones	Elevated infrequently	Normal	Elevated in metastasizing carcinoma of prostate	Elevated
Multiple myeloma	Elevated frequently	Normal	Normal	Slightly elevated

* After Gutman et al.[44]

* Determinations by Dr. Christine Waterhouse, University of Rochester School of Medicine, Rochester, N. Y.

detract from the establishment of such a diagnosis.

Anticomplementary Wassermann (25 per cent). The incidental occurrence of an anticomplementary Wassermann reaction is sometimes the first clue to the discovery of a case of multiple myeloma. This phenomenon is associated with cases in which there is marked hyperproteinemia.

White Blood Count and Peripheral Blood Smear. The white blood count in most of these cases of myeloma was within normal limits (average 8,975 per cu. mm.). Likewise there was little alteration of the differential formula. However, if careful search were made for plasma cells in the peripheral blood, plasma cells were found in small numbers in 25 per cent of the cases in which such a search was made. In two of our cases these cells were present in high percentages, i.e., 62 and 28 per cent. Both cases would have been considered by many to represent cases of plasma cell leukemia. In our opinion, however, there is reason to consider that these two cases represent a variant of the same underlying condition, namely, multiple myeloma.

COURSE

The vast majority of patients in this group pursued a continuous downhill course from the onset of symptoms to the time of death. We have not seen what would be considered a true remission as has been reported elsewhere. Prior to admission to the hospital the average duration of symptoms was nine months. The patient remained in the hospital on the average of forty-three days and the average prognosis from the onset of symptoms was twenty-one months. The longest survival time was five years; the shortest one month.

DIFFERENTIAL DIAGNOSIS

The commonest diseases which were confused with multiple myeloma in this series in order of frequency were: metastatic malignancy to bone, arthritis (rheumatoid, degenerative or infectious), anemia (pernicious or iron-deficiency), chronic nephritis, undulant fever, hyperparathyroidism, Paget's disease, ruptured nucleus pulposus, osteomyelitis, leukemia and tuberculosis. Space does not permit a discussion of the differential diagnosis of each of these conditions but it will be seen that the above diseases fall into four main groups: (1) disease of bone; (2) the anemic states; (3) renal disease; (4) certain febrile illnesses. In general, it can be said that the one factor which aided most, either directly or indirectly, in the differential diagnosis of multiple myeloma was the occurrence of abnormalities of the plasma proteins.

The differential diagnosis of disease of the bone is aided materially by a careful study of the serum calcium and inorganic phosphorus levels and a determination of the alkaline and acid phosphatase activity. (Table III.) When this information is added to careful roentgenographic interpretation, much confusion may be averted.

The elucidation of unexplained anemia, whether it be macrocytic, normocytic or microcytic, is aided by the examination of a suitable bone marrow preparation taken from the sternum. Such conditions as pernicious anemia in relapse and iron-deficiency anemia are thereby easily differentiated. As has been stated previously, in only five cases were negative results obtained in a case which later proved to be multiple myeloma.

The differential diagnosis of chronic renal disease is often confusing. However, the frequent occurrence of Bence Jones proteinuria, the low incidence of hypertension and the inability to demonstrate renal disturbance by roentgenographic means all contribute to our ability to distinguish the renal insufficiency of multiple myeloma from other renal disorders.

Various febrile illnesses (undulant fever, tuberculosis, etc.) may be confused with multiple myeloma unless it is realized that fever is a common accompaniment of the latter disease. It is not our intention to give a differential diagnosis of all the febrile illnesses but merely to emphasize that such

illnesses are frequently confused with multiple myeloma.

TREATMENT

Recently Snapper[45,46,47] has published a series of articles on the effect of stilbamidine and related substances in the treatment of multiple myeloma. No claim is made as to cure of the disease but it has been found that following administration of this drug the patient's pain is frequently alleviated and the roentgenographic spread of the bone lesions is noted to be brought to a temporary halt. We have had limited experience with this type of therapy but such investigation is in progress at the present time at this clinic.

The judicious use of roentgen therapy to relieve the intractable bone pain to which these patients are prone has met with considerable success. It is also interesting to note that the longest survival time (five years) occurred in a patient who received a large amount of x-ray during the course of his disease.

General considerations as to treatment include guarding against too strenuous activity because of the likelihood of pathologic fracture, the maintenance of proper oral hygiene and the judicious use of supportive measures.

CONCLUSIONS

From the experience gained from the study of these cases we conclude that the incidence of plasma cell tumors is greater than had been previously suspected. It is the responsibility of the clinician to recognize the cardinal signs and symptoms of this condition and to request the proper laboratory studies which may corroborate such a diagnosis. It is self-evident that unless the existence of the disease is suspected by the clinician its "accidental" laboratory discovery will be rare indeed. In our present state of knowledge very little of a specific nature can be done for these patients. However, in the interests of making earlier and more accurate diagnoses than in the past, the following suggestions are made: First, that in any case in which either hyperproteinemia or hyperglobulinemia is discovered, careful electrophoretic studies be carried out. Second, that more attention be paid to the occurrence of rouleaux formation of the red blood cells in the peripheral blood and to the bright blue coloration of the Wright's stained blood smear, and that a satisfactory cause for their presence be found. Third, that any case of unexplained anemia (particularly in the older age groups) be given the benefit of a sternal aspiration and/or sternal biopsy. Fourth, that more energetic and careful searches be made for Bence Jones protein in all urine specimens which contain protein. Fifth, that the level of serum calcium, inorganic phosphorus, alkaline and acid phosphatase be determined in suspicious cases. Sixth, that careful analysis be made of all roentgenographic osteolytic processes and more attention be paid to the occurrence of osteoporosis.

In fifteen cases of myeloma the electrophoretic patterns were similar to those previously reported in this disease. In six cases there was a tall, narrow, abnormal peak migrating more slowly than gamma globulin. This type of pattern had not, to our knowledge, been previously reported. The patterns of these twenty-one cases would in all except one instance justify a presumptive diagnosis of multiple myeloma. Eight cases showed patterns of another type not previously reported. Large abnormal peaks were absent, but there were significant small abnormalities. In six cases of this group the patterns were believed to be strongly suggestive of myeloma. In the two other cases the patterns were only suggestive of some form of malignant disease. In this group of eight cases the incidence of Bence Jones proteinuria was 87.5 per cent. It is suggested that in many cases in which large abnormal peaks are absent, small abnormalities are due to Bence Jones protein in the plasma. The high incidence of Bence Jones proteinuria in this group may result from the absence in the plasma of a

high molecular weight protein capable of forming complexes with Bence Jones protein.

SUMMARY

An analysis of sixty-one cases of plasma cell tumors is given. Particular attention is devoted to the electrophoretic patterns which occur in this condition and suggestions are made which may increase the accuracy and promptness of the diagnosis of this type of tumor. The electrophoretic patterns of twenty-nine consecutive cases of diffuse plasma cell tumor were all abnormal. One case of solitary myeloma of the antrum with low grade chronic infection gave patterns which were normal except for those changes which commonly accompany infection. Five abnormal patterns from cases other than myeloma which might be confused with those of multiple myeloma are shown.

REFERENCES

1. Bence Jones, H. On a new substance in the urine of a patient with mollities ossium. *Phil. Tr. Roy. Soc. London*, 138: 55, 1848.
2. Dalrymple, J. On the microscopical character of mollities ossium. *Dublin Quart. J. M. Sc.*, 2: 85, 1846.
3. MacIntyre, W. Case of mollities and fragilitas ossium, accompanied with urine strongly charged with animal matter. *Med.-chiur. Tr.*, 33: 211, 1850.
4. Von Rustizky, J. Multiples Myelom. *Ztschr. f. Chir.*, 3: 162, 1873.
5. Kahler, O. Zur Symptomatologie des Multiplen Myeloms: Beobachtung von Albumosurie. *Prague Med. Wchnschr.*, 14: 33, 1889.
6. Ellinger, A. Das Vorkommen des Bence-Jones'-schen Körpers im Harn bei Tumoren des Knochenmarks und seine diagnostiche Bedeutung. *Deutsches Arch. f. klin. Med.*, 62: 254, 1889.
7. Jacobson, V. C. A case of multiple myelomata with chronic nephritis showing Bence Jones protein in urine and blood serum. *J. Urol.* 1: 167, 1917.
8. Longsworth, L. G., Shedlovsky, T. and MacInnes, D. A. Electrophoretic patterns of normal and pathological human blood serum and plasma. *J. Exper. Med.*, 70: 399, 1939.
9. Slavens, J. J. Multiple myeloma in a child. *Am. J. Dis. Child.*, 47: 821, 1934.
10. Bayrd, E. D. and Heck, F. J. Multiple myeloma—a review of 83 proved cases. *J. A. M. A.*, 133: 147, 1947.
11. Wintrobe, M. M. and Buell, M. V. Hyperproteinemia associated with multiple myeloma. *Bull. Johns Hopkins Hosp.*, 52: 156, 1933.
12. Atkinson, F. R. B. Multiple myelomata. *M. Press*, 195: 312, 1937.
13. Magnus-Levy, A. Multiple myeloma. *Ztschr. f. klin. Med.*, 126: 62, 1933.
14. Geschickter, C. F. and Copeland, M. M. Multiple myeloma. *Arch. Surg.*, 16: 807, 1928.
15. Batts, M. Jr. Multiple myeloma—review of forty cases. *Arch. Surg.*, 39: 807, 1939.
16. Ghormley, R. K. and Pollock, G. A. Multiple myeloma. *Surg., Gynec. & Obst.*, 69: 648, 1939.
17. Coley, W. B. Multiple myeloma. *Ann. Surg.*, 93: 77, 1931.
18. Moschkowitz, E. Essays on the biology of disease-myeloma. *J. Mt. Sinai Hosp.*, 13: 205, 1946.
19. Svedberg, T. and Sjøgren, B. The molecular weight of Bence Jones protein. *J. Am. Chem. Soc.*, 51: 3594, 1929.
20. Svedberg, T. and Pedersen, K. O. The Ultracentrifuge. Oxford, 1940. Clarenden Press.
21. Magnus-Levy, A. Über krystallisiertes und amorphes Bence Jones Eiweiss. Multiple myelome. IX. *Ztschr. f. physiol. Chem.*, 243: 173, 1936.
22. Bayne-Jones, S. and Wilson, D. W. Immunological reactions of Bence Jones proteins. I. Differences between Bence Jones proteins and human serum proteins. *Bull. Johns Hopkins Hosp.*, 33: 37, 1922. II. Differences between Bence Jones proteins from various sources. *Ibid.*, 119, 1922.
23. Hektoen, L. and Welker, W. H. Immunological differences of crystalline Bence Jones proteins. *J. Biochem.*, 34: 487, 1940.
24. Moore, D. H., Kabat, E. A. and Gutman, A. B. Bence Jones proteinemia in multiple myeloma. *J. Clin. Investigation*, 22: 67, 1943.
25. Gutman, A. B., Moore, D. H., Gutman, E. B., McClellan, V. and Kabat, E. A. Fractionation of serum proteins in hyperproteinemia with special reference to multiple myeloma. *J. Clin. Investigation*, 20: 765, 1941.
26. Snapper, I. Medical Clinics on Bone Diseases. P. 181. New York, 1943. Interscience Publishers, Inc.
27. Kekwick, R. A. The serum proteins in multiple myelomatosis. *Biochem. J.*, 34: 1248, 1940.
28. Longsworth, L. G. Recent advances in the study of proteins by electrophoresis. *Chem. Rev.*, 30: 323, 1942.
29. Longsworth, L. G. A modification of the schlieren method for use in electrophoretic analysis. *J. Am. Chem. Soc.*, 61: 529, 1939.
30. Zeldis, L. J. and Alling, E. L. Plasma protein metabolism—electrophoretic studies. Restoration of circulating protein following acute depletion by plasmophoresis. *J. Exper. Med.*, 81: 515, 1945.
31. Stern, K. J. and Reiner, M. Electrophoresis in medicine. *Yale J. Biol. & Med.*, 19: 67, 1946.
32. Shapiro, S., Ross, V. and Moore, D. H. A viscous protein obtained in large amounts from the serum of a patient with multiple myeloma. *J. Clin. Investigation*, 22: 137, 1943.
33. Pedersen, K. O. Ultracentrifugal studies on serum and serum fractions. Almqvist and Wiscksells Boktryckeri, A. B. Uppsala.
34. Martin, N. H. A study of the plasma and tissue globulins in myelomatosis. Program Thirty-ninth Annual Meet., Am. Soc. Clin. Investigation, p. 23. May 5, 1947.

35. WINTROBE, M. M. Clinical Hematology. Philadelphia, 1946. Lea and Febiger.
36. FAIRMAN, E. and WHIPPLE, G. H. Bone marrow volume in adult dogs. *Am. J. Physiol.*, 104: 352, 1933.
37. HEWSON. Experimental enquiries. 3: 28, 1777.
38. DESENAC. Traité de la Structure du Coeur Livre. 2nd ed., p. 5, 1783.
39. HOME, E. On the changes the blood undergoes in the act of coagulation. *Phil. Tr. London*, 108: 176, 1818.
40. WHARTON-JONES, T. On the state of the blood and the blood vessels in inflammation. *Guy's Hosp. Rep.*, 7: 1, 1851.
41. REIMANN, H. A. Hyperproteinemia as a cause of autohemagglutination. *J. A. M. A.*, 99: 1411, 1932.
42. FÅHREUS, R. The suspension stability of the blood. *Acta med. Scandinav.*, 55: 1, 1921
43. BLACKMAN, S. S., JR., BARKER, W. H., BUELL, M. V. and DAVIS, B. D. On the pathogenesis of renal failure associated with multiple myeloma. Electrophoretic and chemical analysis of protein in urine and blood serum. *J. Clin. Investigation*, 23: 163, 1944.
44. GUTMAN, A. B., TYSON, T. L. and GUTMAN, E. B. Serum calcium, inorganic phosphorus, and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of bones. *Arch. Int. Med.*, 57: 379, 1936.
45. SNAPPER, I. On the influence of stilbamidine upon multiple myeloma. *J. Mt. Sinai Hosp.*, 13: 119, 1946.
46. SNAPPER, I. and SCHNEID, B. On the influence of stilbamidine upon myeloma cells. *Blood*, 1: 534, 1946.
47. SNAPPER, I. Stilbamidine and pentamidine in multiple myeloma. *J. A. M. A.*, 133: 157, 1947.

Test for the Presence of the "Hypertensive Diencephalic Syndrome" Using Histamine*

HENRY A. SCHROEDER, M.D. *and* MELVIN L. GOLDMAN, M.D.†
St. Louis, Missouri

PAGE has described a syndrome associated with arterial hypertension which he called the "hypertensive diencephalic syndrome."[1] We quote from his description: "This syndrome was described as occurring usually in young and middle-aged women, though it may be seen occasionally in men. It is characterized by hypertension of the labile sort, more especially by the periodic appearance of a blotchy blush which extends down over the face and upper chest, seldom, if ever, involving the limbs. Indeed, the extremities may be cold, pale or have a dusky, mottled hue during an attack. Over the area of blush are minute beads of perspiration. Lacrimation or merely "watering" of the eyes may occur without an associated emotional counterpart. Tachycardia and hyperperistalsis are common. These episodes occur without apparent cause or may be brought on by embarrassment and excitement."[2]

Penfield[3] first described a syndrome similar to this which occurred in a patient with a tumor of the third ventricle; he called it "diencephalic autonomic epilepsy." Symptoms and signs can be grouped roughly as disturbances of function of three components of the autonomic centers: (1) Emotional instability can be seen by the excessive nervous tension and anxiety from which these patients suffer from time to time as well as attacks of uncontrollable and unreasonable weeping. These latter appear to bear no relation to the patient's inner emotional status at the time of the attack; she is unable to give a reason for her actions which come on spontaneously at any time and which are senseless to her. Many of the less severely disturbed patients do not exhibit these outbursts but may complain of attacks of emotional tension appearing without reason. (2) Vasomotor instability is shown by lability of the blood pressure (even after many years of sustained hypertension), the characteristic blotchy blush on the skin and recurrent episodes of cold, clammy and pale or cyanotic extremities. Blood pressure is usually higher when the blush is present. (3) Autonomic instability is evidenced by excessive perspiration, attacks of emotional polyuria, deep sighing respirations (often seen on the tracing made for determination of the basal metabolic rate) and the occasional presence of low grade fever. Often the patients' only complaints are of attacks of the nature described. Sometimes the headaches from which they suffer occur only during such attacks. We have noticed the presence of this syndrome in certain hypertensive patients for a number of years[4] and have believed with Page that it represented a neurogenic component which could be differentiated from other pathogenic factors.

The curious blotchy rash or blush is the most common characteristic of this syndrome. (Figs. 1 to 3.) We have seen it over the chest and back, upon arms, neck and face but rarely on the abdomen. In women it usually does not appear in the area over the shoulders subject to chronic compression by straps of clothing. Occasionally areas on

* From the Department of Internal Medicine and the Oscar Johnson Institute, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo., under a grant-in-aid from the U. S. Public Health Service, National Institutes of Health.

† National Institutes of Health Postdoctorate Research Fellow.

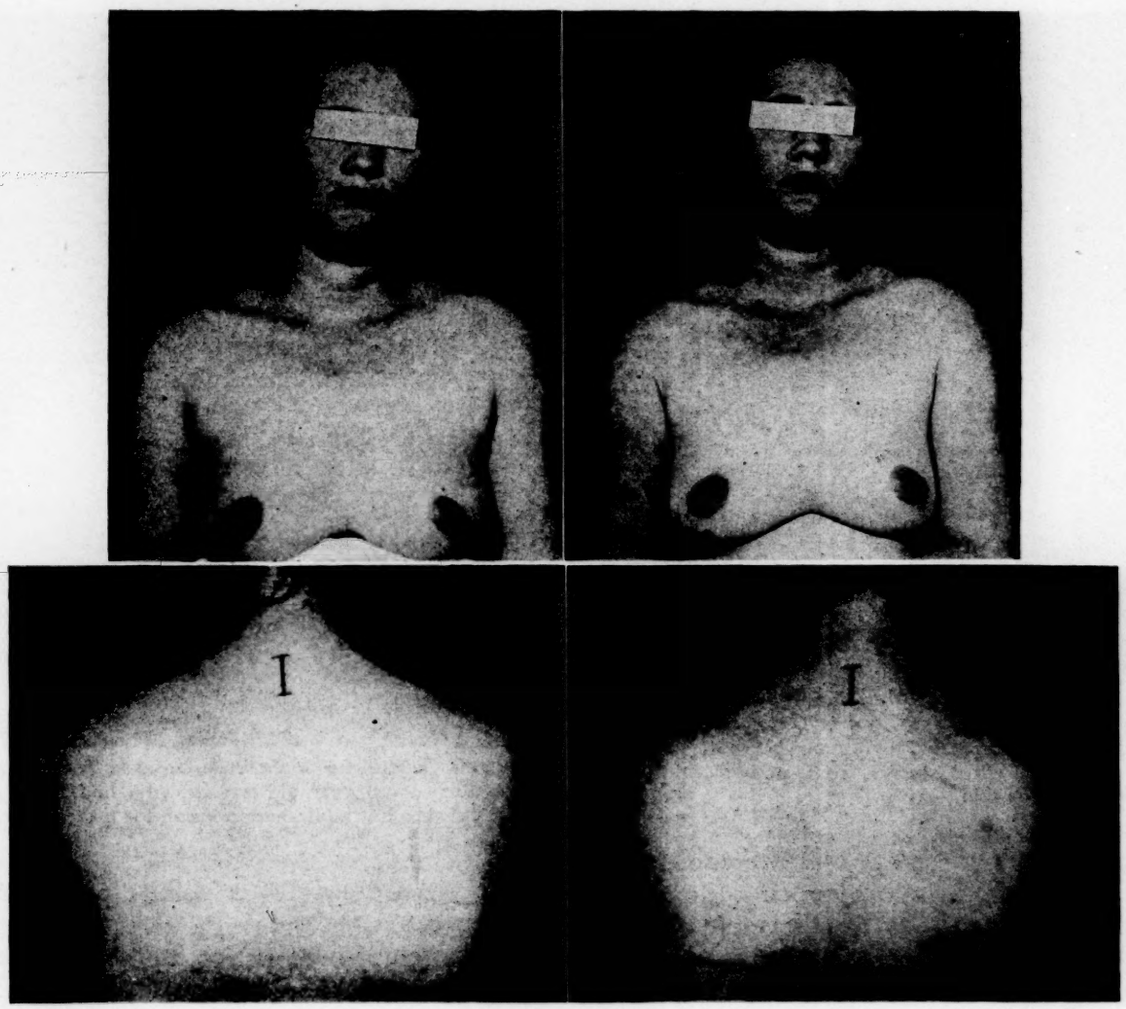


FIG. 1. Blotchy blush appearing ten minutes after the intradermal injection of 0.25 mg. of histamine into the left forearm of a twenty-eight year old woman; A, before B, after injection. Note the rash on the upper arms, neck, back and shoulders; circumoral pallor can be seen faintly; the rash was a bright red. Hypertension was of the labile type. Although this reaction was repeatedly demonstrated, it disappeared after lumbodorsal sympathectomy.

the face are brilliant red or purplish with a sharp line of demarcation next to one which is dead white.

Because this syndrome is common, interesting speculatively and suggests certain manifestations of a discharge of impulses from the hypothalamus through the autonomic nervous system and because it has been reproduced by stimulation of the hypothalamus, a test to bring it out is of some value for studying it further. If these manifestations, dramatic as they are, are concerned with some specific underlying mechanism of certain types of hypertension, such a test might be used to differentiate cases of one variety from another.

Accordingly, attempts were made to reproduce the attacks by a method other than induction of embarrassment or excitement. It was soon found in many cases that histamine injected intradermally would cause the blush and other characteristic symptoms to appear. Therefore, this test was applied to a number of patients, some with normal blood pressures and some with hypertension.

METHOD

With the patient recumbent, 0.25 cc. of histamine acid phosphate solution (0.25 mg. of histamine base) was injected intradermally into the volar surface of the forearm. As this amount of fluid was fairly large

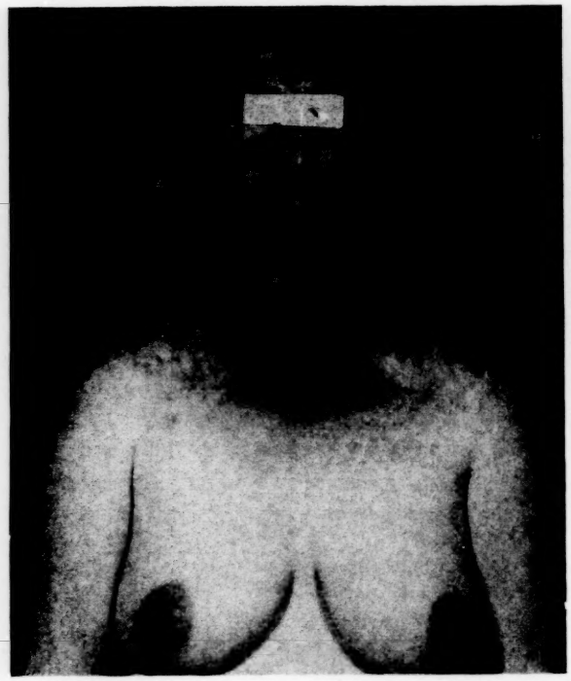


FIG. 2. Blotchy erythema resulting from the intradermal injection of histamine in a thirty-two year old woman exhibiting "neurogenic" hypertension. Note areas on the shoulders where straps from underclothing had compressed the skin.

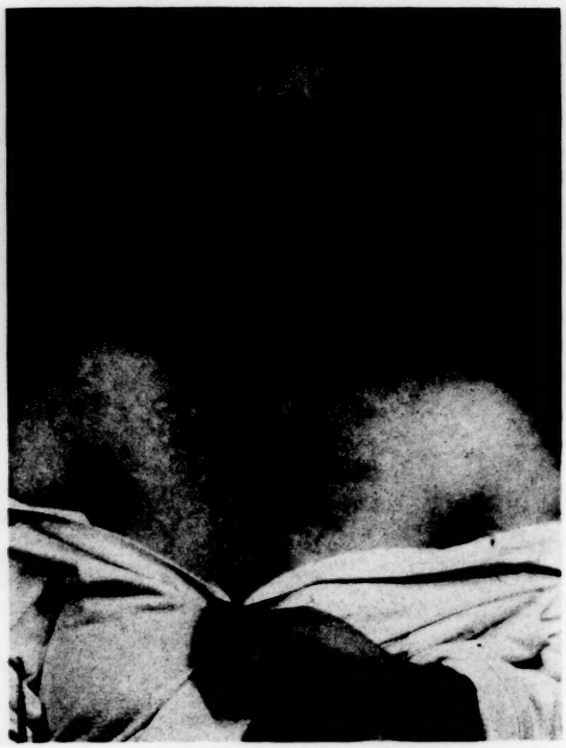


FIG. 3. Typical diencephalic blush induced by emotion in a thirty-seven year old woman who had suffered from a severe but labile hypertension for fifteen years.

some of the material probably escaped into subcutaneous tissues. The injection was accompanied by a sharp, severe pain not unlike that of a bee sting which subsided rapidly. Five, ten and fifteen minutes later patients were examined carefully for skin manifestations and were questioned closely for symptoms. Any complaint similar to those usually experienced (headache, palpitation, etc.) was especially noted. Blood pressure changes were recorded in many by the auscultatory method.

One hundred three ward and clinic patients were so tested, fifty-three of whom suffered from arterial hypertension and fifty did not. There was some tendency to test more patients exhibiting clinical signs of "neurogenic" hypertension because it was soon found that these were the type giving positive responses. Of the hypertensives, sixteen were males and thirty-seven were females; there were twenty-five normotensive males and twenty-five females. An attempt was made to classify them according to a plan previously described.[4]

No attempt was made to control the temperature of the room in which the test was made but it was never excessively cold. No effect of outside temperature or weather was seen in the results.

The following criteria were graded 1 plus to 4 plus: (1) Flushing of the face and circumoral pallor which were present to some degree in most cases and were recorded but not considered in the overall evaluation of the test. (2) Headache; the type, location, severity and duration of which were recorded and graded. Special attention was paid to the resemblance of the headache produced by histamine to that typically experienced as a result of hypertension. (3) Tearing or lacrimation; mere watering of the eyes to uncontrollable outbursts of weeping and sobbing were graded and attention was given to the presence of similar attacks in the history of the patient.

(4) Blotchy erythema; the presence and degree of the mottled blush on the face, back, neckline, chest and abdomen was noted. The presence of a "strap line" of normal skin on the shoulders where compression from undergarments had occurred was recorded. (5) Local reaction; the presence of a wheal and erythema at the site of injection was noted. (6) The total reaction, based upon an evaluation of the aforementioned signs, was graded as negative or 1 plus to 4 plus. The blush was given greatest weight in this estimation.

RESULTS

Sixteen hypertensive patients showed a reaction to histamine considered as 3 or 4 plus. (Table I.) Of these, all were considered to exhibit clinical signs of "neurogenic" hypertension in that blood pressures were labile, vascular disease was minimal, the course was usually benign and there were associated emotional disturbances. Sixteen more patients of a similar type gave a reaction considered as 2 plus, a definite although less marked response. Only seven of this type did not react or reacted only slightly. In addition four patients exhibiting associated disturbances suspected to be of endocrine origin, two suffering from general arteriosclerosis and seven of eight classified in an "unknown" category gave negative to minimal reactions. Only one patient in this group showed a 2 plus reaction. The blush and other symptoms appeared three to five minutes after injection and reached its greatest intensity in ten minutes. It usually lasted fifteen to thirty minutes, fading gradually.

Two patients exhibiting occasional slight elevations of blood pressure were considered to be "prehypertensive." In one patient a marked reaction was elicited and in the other a mild reaction was seen.

Of the normal controls forty patients did not react in this manner to histamine, five reacted slightly and only five showed responses considered 2 to 4 plus. Two of these suffered from psychoneurosis and low grade fever of unknown origin, one of Hodgkins disease, and one of mild rheumatoid arthritis with slight elevation of systolic blood pressure, cold moist extremities and palpitation.

Tests were repeated weeks or months apart in six patients who reacted and similar results were obtained. Three female patients who repeatedly had reacted excessively to the drug were subjected to lumbodorsal sympathectomy; excellent early results were obtained and their blood pressures remained at normal levels. Postoperatively none of them reacted to histamine. A markedly positive response in another disappeared after operation although blood pressure did not fall to normal levels.

TABLE I

RESULTS OF "HISTAMINE TEST" IN ELICITING SIGNS AND SYMPTOMS OF HYPERTENSIVE DIENCEPHALIC SYNDROME

	Reaction					Total	Total Positive*	
	0	+	++	+++	++++		No.	Per Cent
Normotensive subjects:								
Male	22	1	1	1	0	25	2	8
Female	18	4	0	1	2	25	3	12
Hypertensive subjects:								
Neurogenic type								
Male	1	2	7	2	2	14	11	79
Female	2	2	9	4	8	25	21	84
Other types:								
Male	2	0	0	0	0	2	0	
Female	8	3	1	0	0	12	1	8

* Positive includes reactors of ++ or greater.

Attempts were made to block this reaction in one by the use of antihistaminic agents but were unsuccessful although the blush produced was of somewhat less intensity. Epinephrine (0.5 mg.) given subcutaneously in four did not reproduce the train of events nor did acetyl-β-methyl choline chloride (12.5 mg.) or yeast adenylic acid (10 mg.).

Headache typical of that usually experienced was reproduced in fourteen hypertensive subjects by histamine. The remainder did not complain of headaches during the test. In thirteen normotensive individuals headache was initiated; in four

it was severe and similar to that previously experienced. One of these was found to have a chromophobe adenoma of the pituitary.

Attacks simulating presenting symptoms were initiated by histamine in most of those patients in whom the test was positive. Aside from the blush and headache, symptoms included: severe spells of weeping (3 patients), dizziness (6 patients), palpitation (10 patients), excitement and anxiety (2 patients) and tachycardia (4 patients). In no patient was generalized vascular collapse produced.

In two hypertensive subjects intradermal histamine produced symptoms of severe headache, palpitation, tachycardia and elevation of blood pressure similar to those seen in cases of pheochromocytoma after its intravenous use.[5] No blush appeared in these individuals. Opportunity for further study on one patient was not given; the other showed a moderate response to the Roth-Kvale test but exploration failed to reveal a tumor in the adrenal gland.

COMMENTS

The mechanism by which intradermal histamine reproduces attacks of the "hypertensive diencephalic syndrome" is not known. One can speculate that histamine directly stimulates certain elements of the autonomic nervous system, stimulates the same elements indirectly by eliciting some other mediator (for example epinephrine or sympathin), or acts directly on skin, nerve tissue and blood vessels. Since epinephrine itself did not produce these symptoms it is unlikely that the mechanism is the same as that suggested by Roth and Kvale for patients with pheochromocytoma.[5] Reproduction of the typical hypertensive headache in a certain proportion of cases suggests that histamine may be concerned in some manner with these headaches, as well as with other symptoms of which these patients complain.

Whether incomplete metabolism of histidine is present in some cases of arterial hypertension is not known but might be suspected by analogy from the work of Holtz.[6] However, we have not seen a positive histamine test in patients with severe renal impairment secondary to hypertension.

This test has been of some value in estimating the degree and presence of the "neurogenic" element in cases of arterial hypertension. Strongly positive reactions were seen only in this type. While the series is small, the results suggest that some such test as this may be of aid in differentiating certain types of individuals from others. Whether it will be of value in the selection of patients for sympathectomy remains to be proven; in a small series operated upon in this hospital, three of the best immediate results were in patients reacting strongly to this test.

Like all such procedures the results are not clear-cut, and the criteria for their evaluation inexact. But from a superficial analysis one can assume that if patients react strongly to histamine in the manner described, they are likely to have a fluctuating blood pressure, a relatively benign course, relatively little renal disease, attacks similar to that produced by the test, and general vascular and emotional lability.

SUMMARY

A test using the intradermal injection of 0.25 mg. of histamine has been described which appears to reproduce attacks typical of the "hypertensive diencephalic syndrome." It also reproduces in some hypertensive patients other symptoms of which they complain. Few normotensive patients respond to histamine in this manner. It is suggested, therefore, that histamine-like substances may be concerned in the causation of some of the symptoms common to many hypertensive patients, especially those exhibiting the "neurogenic" type.

Acknowledgment. The authors are indebted to Dr. Palmer H. Futcher and Dr. John A. Nuetzel for performing some of the tests. Photographs in Figs. 1 and 2 were made by Mr. K. Cramer Lewis of the Department of Illustration, Washington University School of Medicine, and

in Fig. 3 by Mr. Joseph B. Haulenbeek of the Rockefeller Institute.

REFERENCES

1. Page, I. H. A syndrome simulating diencephalic stimulation occurring in patients with essential hypertension. *Am. J. M. Sc.*, 190: 9, 1935.
2. Page, I. H. and Corcoran, A. C. Arterial Hypertension, Its Diagnosis and Treatment. Chicago, 1946. The Year Book Publishers.
3. Penfield, W. Diencephalic autonomic epilepsy. *Arch. Neurol. & Psychiat.*, 22: 358, 1929.
4. Schroeder, H. A. and Steele, J. M. Studies on "essential" hypertension. I. Classification. *Arch. Int. Med.*, 64: 927, 1939.
5. Roth, G. M. and Kvale, W. F. Tentative test for diagnosis of pheochromocytoma. *J. Lab. & Clin. Med.*, 30: 366, 1945.
6. Holtz, P., Credner, K. and Walter, H. Über die Spezifität der Aminosäuredecarboxylasen. *Ztschr. f. physiol. Chem.*, 262: 111, 1939.

Treatment of Thromboangiitis Obliterans

Two-year Follow-up after Sympathectomy

WILLIAM J. MESSINGER, M.D.,* EDMUND N. GOODMAN, M.D.*
New York
and JAMES C. WHITE, M.D.†
Boston, Massachusetts

In a previous report Goodman, Messinger and White[1] reported their experiences with patients favorably influenced by intervention on the autonomic nervous system. The immediate results achieved in thromboangiitis obliterans were so impressive that it was decided to sympathectomize all new proven cases in which high vasoconstrictor tone could be demonstrated and to subject these individuals to periodic review in order to gauge the long term effectiveness of treatment. This report is concerned with an evaluation of nineteen patients with thromboangiitis obliterans treated by sympathectomy.

METHODS OF STUDY

These were as described in our previous report,[1] with the following additions: A psychiatrist was invited to participate in the evaluation of patients. Photographs of the involved extremities of all patients were obtained in color prior to and following sympathectomy as objective records. Since blocking of the paravertebral ganglia by means of procaine taxes the patient, personnel and facilities, tetraethyl ammonium chloride,‡ a drug which blocks the autonomic ganglia, in the dosage of 7 to 10 mg. per Kg. intravenously was employed and proved to be an acceptable substitute. The pharmacologic properties of this drug have been the subject of previous reports by Lyons et al.[2] The side-effects of the drug sometimes incapacitated a patient temporarily, rendering him unfit for immediate ambulation.

When the effect of sympathectomy on the patients' claudication time was investigated, procaine block of the paravertebral sympathetic ganglia was again the procedure used. In an attempt to obtain evidence of increased deep blood flow of the extremities following sympathectomy we recently have been subjecting all new patients before and after operation to the ergometric procedure reported by Hitzrot et al.[3] These results will be the subject of a future report. Finally, to evaluate properly some individuals with vague extremity pain we found the technic of Naide[4] to be most useful in excluding bizarre vascular manifestations of early arthritis. Patients with massive gangrene or infection were treated initially in the manner described in our previous report.

Surgical Technic. For lumbar sympathectomy the patient is placed in a lateral position with knees bent and hips flexed. A hockey-stick-type incision is used, extending from the border of the semispinalis muscle at the level of the twelfth rib to a point 2.5 cm. above the anterior superior spine of the ilium. A portion of the external oblique muscle is cut, the transversalis fascia split and the lumbodorsal fascia incised. The retroperitoneal space is thus exposed and the abdominal contents are stripped forward simply by hugging the quadratus lumborum and psoas muscles. The sympathetic chain can now be visualized at the junction of the psoas muscle and vertebral body. Due caution must be exercised to prevent injury to the ureter and the vena cava on the left and aorta and ureter on the right. With the aid of a long nerve hook, the sympathetic chain is held and the individual rami of the ganglia to be removed are clipped with silver brain clips and the chain proximal and distal to the ganglia doubly clipped prior

* Now on the Vascular and The Neurosurgical Services, U.S.N.H., St Albans, N. Y.
† Now on the Neurosurgical Service, Massachusetts General Hospital, Boston, Mass.
‡ Etamon, generously supplied by Parke, Davis & Co.

to resection of the ganglia. Silk closure is used with all spaces closed tightly and air-free.

A prerequisite for thoracic sympathectomy is intratracheal anesthesia. The patient is placed in a prone position with a pillow under his chest to accentuate the upper thoracic spinal curve while the arms are allowed to fall free in order to throw the scapulae anteriorly. At the level of T_1 an 8 cm. incision is made, extending to the level of T_4, 4 cm. lateral to the spinous processes. A 4 cm. section of the third rib is removed from its vertebral attachment. The endothoracic fascia can now be incised, pleura and lung retracted from the rib surfaces and the area from first to fourth rib exposed. The second and third intercostal nerves are identified and their communicating rami with the sympathetic chain are divided. By exerting gentle traction on the intercostal nerves the anterior and posterior roots are brought into view and the nerves severed at their emergence from the intervertebral foramina. The sympathetic chain, held with a nerve hook, is divided below the fourth ganglia and the length of the chain, including the second, third and fourth ganglia, is covered with tantalum foil so that the distal end is capped and bent on itself. The chain is then anchored into the semispinalis muscle in a cephalad direction. The use of the foil in this manner and the diversion of the chain in the cephalad direction are emphasized since we believe the maneuver effectively prevents regeneration in most instances.

Distribution of Cases. All of our patients were males, all were smokers. Significantly, they indicated a one- to threefold increase in smoking either upon entrance into service or since release from service. The colored race was not represented, but no special racial distribution was apparent. The youngest patient was twenty years and the oldest fifty-four years of age. The symptoms and findings of each patient are recorded briefly in Table I. The presence of Raynaud's syndrome, of migratory phlebitis and of involvement of all four extremities in this group approximates the incidence reported in a larger series of cases by Freeman[5] from the Army Vascular Centers. The presence of epidermophytosis in some of these patients may have been contributory to their phlebitis. It is more likely that the increased growth of the fungus was due to hyperhidrosis and the vein involvement a primary manifestation of the underlying vascular disease. It should be noted that all of our patients were either Navy personnel or veterans of the services.

RESULTS

No patient's symptoms were worse after operation and no fatalities occurred due to operation. Pain in all patients subjected to operation was relieved within forty-eight hours after the procedure was carried out so that the use of narcotics and analgesics could be discontinued as soon as discomfort from the operative site ceased. Reversal of color changes started immediately after operation and ulcerated gangrenous areas generally began to heal promptly. In a few patients color changes and symptoms became worse five to seven days following operation. This was of short duration and thought to be due to the transient burst of vasoconstrictor and sudomotor activity that generally occurs at this time after any peripheral sympathetic denervation. This phenomenon had been previously described by White and Smithwick.[6] There were no amputations in this series. No patient was bedridden more than four days because of the operative procedure. All patients except one (Case XVIII) reported significant amelioration of claudication (when present) within a week after operation and progressive improvement thereafter. In this connection it is only fair to state that in those with long-standing symptoms and muscle wasting, complete rehabilitation was naturally of longer duration. It is true nevertheless that the majority of our patients were able to return to work in four to six weeks without recourse to further medical treatment. Signs of nerve regeneration have not appeared in this group.

Since the preservation of sexual function in the age groups found in this series was of some concern to the patients, the first lumbar ganglion was spared whenever possible. As our experience accumulated it became apparent that the first lumbar ganglia were not of prime importance for the preservation of erection and ejaculation. This observation was significant because

these ganglia control the important area from knee to hip. To summarize our observations concerning sexual disturbances resulting from lumbar sympathectomy in over one hundred cases we can state the following: No patient reported permanent disturbance of erection or ejaculation as a result of unilateral operation when L_1 was included in the ganglia removed. Practically all patients reported disturbances after bilateral operation. These consisted of failure of erection, loss of ejaculation or both although L_1 was excluded in some instances. Between these extremes various complaints were noted, none of which appeared to incapacitate the individual's sexual powers permanently. We therefore can conclude from our observations that no single lumbar ganglion controls the sexual functions and that these functions most likely are mediated bilaterally through the lumbar ganglia. Unfortunately, we have no reliable data with regard to sterility in these individuals after operation.

COMMENTS

Silbert,[7] who has followed more than 500 individuals with this disease from two to fifteen years, has indicated that cessation of smoking will cause the disease to be self-limiting, and in some early cases this alone appears to be sufficient to result in relief of symptoms. We believe that there is general agreement with this statement. It should also be self-evident from the reports on the multiplicity of medicinal, thermal and mechanical agents used in the treatment of this disease that the patient requires further therapy after he gives up use of tobacco.

In the light of newer knowledge concerning peripheral blood flow, re-examination of the evidence forming the basis for some of the medicinal treatments in thromboangiitis obliterans appears to be in order. For example, Friedlander et al.,[8] using muscle and skin thermocouples, reported that after such procedures as reflex body heating, block of the sympathetic ganglia by procaine and spinal anesthesia, skin temperature increased while muscle temperature remained unchanged. Intravenous injection of 300 cc. of 5 per cent sodium chloride caused both increase in muscle and skin temperature. That muscle temperature changes can be used as an index of muscle blood flow has been challenged by Wilkins[9] and most recently by Barcroft and Edholm.[10] These investigators oppose such inferences since muscle is so much less vascular than skin that the release of vasoconstrictor tone causes far less increase in blood per unit volume of tissue than it does in skin. In addition they emphasize the fact that unless every precaution is taken to prevent cooling of the limb prior to sympathetic block the muscle blood flow would be subnormal and the effect of the block reduced.

All our patients with thromboangiitis obliterans were found to be inveterate smokers. This situation prevailed despite the fact that they had been persistently warned against smoking. It was gratifying to note in eleven of our patients apparent reversal of this attitude after sympathectomy. We do not doubt that some will again return to the habit, not because of recurrence of symptoms but mainly because of the social amenities and modern advertising practices. This seems to be confirmed in our follow-up. (Table I.)

Surgical interruption of sympathetic pathways for thromboangiitis obliterans does not originate with us. Harris,[11] Freeman and Montgomery,[12] Leriche[13] and deTakats[14] are among those whose reports indicate that the procedure has a favorable influence on the course of this disease. In a report summarizing the Army's wartime experience in its vascular disease centers, Freeman[5] states that 53 of 160 patients with thromboangiitis obliterans were treated by sympathectomy. Of these three failed to improve and these were patients who continued to smoke. In this connection a brief review of the history of Case XVIII is interesting since this patient failed to maintain his

TABLE I

TREATMENT OF THROMBOANGIITIS OBLITERANS WITH SYMPATHECTOMY

Case No.	Name	Age	Symptoms	Duration	Pertinent Findings	Operation	Two-year Follow-up
I	S. B.	22	Calf and foot pain bilaterally upon walking, relieved by rest	?	Absent pedal pulses; diminished calf oscillometric readings; cool hyperhidrotic feet; marked blanching on elevation; marked delay in vein filling in dependency	Bilateral lumbar sympathectomy, L_2, L_3	Warm, dry feet immediately after operation; asymptomatic and not smoking
II	P. C.	23	Raynaud's syndrome of both lower extremities with hyperhidrosis; severe calf pain on walking, also Raynaud's syndrome of upper extremities	2 yr.	Pallor and numbness of feet on elevation and rubor on dependency; diminished post-tibial and dorsalis pedis pulsations; pallor of both hands on elevation and rubor on dependency; diminished right radial pulsation and poor ulnar collaterals on left	Bilateral lumbar sympathectomy, L_2, L_3; bilateral thoracic sympathectomy, T_2, T_3, T_4 and second intercostal nerve rhizotomy	Immediate reversal of color changes in all extremities after operation; occasional pain in legs in cold weather; unlimited exercise tolerance. Dorsalis pedis pulses remain diminished but left ulnar collateral circulation is good; smoking
III	C. D.	24	Numbness, pain and coldness of fingers and toes; ulceration of fingertips of 3 months' duration	5 mo.	Marked hyperhidrosis of hands and feet with severe color changes upon change in position; ulceration of all fingertips; all major pulse diminished in the upper and lower extremities, left posterior tibial and both dorsal pedis pulses absent	Bilateral lumbar sympathectomy, L_2, L_3; bilateral thoracic sympathectomy, T_2, T_3, and second intercostal nerve rhizotomy	Prompt healing of finger ulcerations after operation and reversal of color changes; good exercise tolerance; no increase in major pulsations; not smoking
IV	M. D.	24	Claudication walking 2 blocks; necrotic ulcer, paronychia 4th left toe	3 mo.	Cold sweaty feet with cyanosis on dependency, blanching on elevation; absence of dorsalis pedis and post-tibials bilaterally, and right popliteal; oscillometric readings diminished in right calf and both feet	Bilateral lumbar sympathectomy, L_2, L_3	Prompt healing of ulcer with early loss of claudication; not smoking; asymptomatic; major pulsations have not returned; no color changes
V	D. E.	45	Numbness of feet; aching of legs and feet on walking; discoloration of feet while dependent, left worse than right	17 yr.	Cold cyanotic feet with diminished skin temperature; all pulses except femorals absent; femoral pulses diminished; no calcification of arteries in legs by x-rays; biopsy of left posterior tibial artery reported as pathognomonic of thromboangiitis obliterans	Transabdominal sympathectomy, L_2, L_3, L_4	Has required no further medical attention; feet are warm and dry and of good color; progressive exercise tolerance without claudication; not smoking

TABLE I (*Continued*)

Case No.	Name	Age	Symptoms	Duration	Pertinent Findings	Operation	Two-year Follow-up
VI	C. F.	36	Swelling, redness and pain in both feet; claudication upon walking 2 blocks	3 yr.	Marked color change and coldness of lower extremities; absence of all pulsations, except the femorals which were diminished; both radial pulses diminished and ulnar collateral circulation poor	Bilateral lumbar sympathectomy, L_1, L_2, L_3, L_4	Progressive relief of claudication and reversal of color changes in lower extremities; feet are warm, dry and painless; both hands are cool and hyperhidrotic; there is beginning ulceration of the tip of the 5th finger, left hand; patient requests thoracic sympathectomy; smoking
VII	H. F.	43	Pain and discoloration of feet; claudication of left calf; one episode of Raynaud's syndrome involving 4th and 5th fingers, left hand	Left leg, 5 yr.; right leg, 3 yr.	Both feet are blue, cold, and hyperhidrotic; changes are more severe in the left foot; only femoral pulses palpable; chronic area of dermatitis present on left ankle	Left lumbar sympathectomy, L_2, L_3	Patient ceased smoking immediately after operation; progressive loss in claudication noted; color changes in left foot became minimal; after 3 weeks the foot became warm and dry; color changes in right foot became minimal in 4 months but the foot remained cool and hyperhidrotic; returned 2 years after operation because of thrombophlebitis of right calf directly related to resumption of smoking; left foot warm and asymptomatic; working up to time of thrombophlebitis
VIII	S. J.	20	Pain and swelling of left foot	?	Absent pedal pulses and left posterior tibial; ulcerations of left 4th and 5th toes; both feet cold and cyanotic; marked pallor on elevation of feet with slow return of color on dependency	Left lumbar sympathectomy L_2, L_3	Immediate warming of left foot with loss of pain after operation; prompt healing of ulcerations; right foot is cool and moist now but left is warm and dry; no color changes in either; asymptomatic; not smoking
IX	R. K.	45	Increasing claudication, left calf; cold, wet left foot	1 yr.	Left calf 3.5 cm. less in diameter than right both dorsalis pedis, left posterior tibial and left popliteal pulsations absent; cool feet with marked rubor and tenderness of first toe, left foot	Left lumbar sympathectomy, L_1, L_2, L_3	Marked relief of symptoms immediately after operation; reversal of color changes in left foot; claudication has progressively decreased so that he can play golf without symptoms; not smoking

TABLE I (*Continued*)

Case No.	Name	Age	Symptoms	Duration	Pertinent Findings	Operation	Two-year Follow-up
x	A. L.	43	Right hand cold and hyperhidrotic; marked blanching and rubor	6 mo.	Necrotic ulcerations of the fingertips 2–5, right hand; right ulnar pulse absent, radial diminished; marked hyperhidrosis of right hand	Right thoracic sympathectomy, T_2, T_3 and 2nd intercostal nerve rhizotomy	Right hand warm and dry; no change in pulsations; ulcerations healed promptly after operation; left hand hyperhidrotic and left ulnar pulse absent; Raynaud's phenomena of left hand; both post-tibial pulses very faint but denies leg symptoms; requests left thoracic sympathectomy; smoking
xi	J. L.	36	Painful, cold, discolored fingers right hand; painful right leg with 2 block calf claudication	14 mo.	Evidence of migrating phlebitis in lower extremities; cold, tender ulcerated right 4th and 5th fingers with color changes; marked tenderness over right ulnar artery; decreased oscillometric readings on left forearm; moderate rubor of both feet; absent dorsalis pedis and posterior tibial pulses	Bilateral lumbar sympathectomy, L_1, L_2; bilateral thoracic sympathectomy, T_2, T_3, T_4 and 2nd intercostal nerve rhizotomies	Immediate relief of pain in hands after operation; rapid loss of claudication and healing of finger ulcers; gradual reversal of color changes; rarely smokes and is asymptomatic
xii	E. M.	43	One half block claudication of both legs; numbness and tingling of the hands with episodes of Raynaud's syndrome of 1st, 2nd and 3rd fingers	6 mo.	Marked dermatophytosis of feet and hyperhidrosis of hands and feet; left radial pulse absent and 2nd and 3rd fingers cold and blue; both posterior tibial arteries barely palpable; no calcification of extremity vessels noted by x-ray	Bilateral thoracic sympathectomy, T_2, T_3 and 2nd intercostal nerve rhizotomies; bilateral lumber sympathectomy, L_1, L_2	Immediate relief of hand symptoms; can walk 1 mile in cold weather without claudication; coldness of 2nd and 3rd fingers, left hand which persists but color is good; posterior tibial pulsations are improved and confirmed by oscillometric readings. Smoking
xiii	P. O'C.	36	Bilateral claudication with coolness and discoloration of the feet; one episode of Raynaud's syndrome right hand; 2 episodes of phlebitis, left leg	18 mo.	Marked color changes and hyperhidrosis of both feet; only femoral pulses palpable; marked delay in vein filling	Bilateral lumbar sympathectomy, L_1, L_2	Dry, warm, lower extremities immediately after operation; rapid reversal of color changes with nearly normal vein filling; major pulses have not returned; gradual diminution in claudication; not smoking
xiv	J. R.	38	Pain and ulceration of 1st toe, right foot	7 mo.	Right foot violaceous in color with a necrotic ulcer extending into the base of the 1st joint; both dorsalis pedis pulses absent in addition to the right posterior tibial	Right lumbar sympathectomy, L_1–L_4; disarticulation of terminal phalanx	Immediate results were good; now has bilateral caludication, worse in left calf., right foot is warm with better vein filling than left; denies smoking

TABLE I (*Continued*)

Case No.	Name	Age	Symptoms	Duration	Pertinent Findings	Operation	Two-year Follow-up
XV	L. R.	33	Said to have had trench foot in 1944; pain, swelling, redness and coldness of the 1st and 2nd toes of left foot	2 wk.	Swelling and rubor of left foot; left foot cold, right cool; draining ulcerations present on tips of 1st and 2nd toes, left foot; left dorsalis pedis and posterior tibial pulses absent; left foot markedly hyperhidrotic; no stigmas of trench foot found	Left lumbar sympathectomy, L_1, L_2	Toe ulcers had healed within 3 wk. after operation; feet are warm, dry and pink with minimal blanching of left foot on elevation; left posterior tibial artery faintly palpable; rarely smokes now
XVI	H. W.	33	Cyanosis, swelling and tenderness of left foot	1½ yr.	Cyanotic, cold left foot; dorsalis pedis pulses absent bilaterally; absent left posterior tibial pulse; severe blanching of left foot on elevation with slow return of color on dependency	Left lumbar sympathectomy, L_1, L_2, L_3	Warm, painless foot immediately after operation; asymptomatic; posterior tibial pulse is palpable; unlimited exercise tolerance; not smoking
XVII	L. W.	54	Claudication, both legs and feet; ulceration of 3rd toe right foot of 1 week's duration; original diagnosis of thromboangiitis obliterans of left lower extremity made at Mt. Sinai Hospital more than 20 yr. ago; original history includes migratory phlebitis and Raynaud's syndrome of lower extremities; insists he has not smoked in 20 yr.	29 yr.	All pulses except femorals absent in lower extremities; right femoral pulse markedly diminished; both feet cool with marked color changes present; nail absent (surgically) from 3rd right toe and a large ulcer present in the nail bed; calcification of larger arteries in lower extremities present by x-ray	Right lumbar sympathectomy, L_2, L_3	Ulcer healed promptly after operation; about 50 per cent improvement in claudication time on right with less color changes; right foot is warm and dry; requests operation on left side; not smoking
XVIII	N. W.	34	Migratory phlebitis, left leg; claudication in left leg within 2–3 blocks of walking	14 mo.	Both feet cool and hyperhidrotic; moderate color changes present in the left foot; both dorsalis pedis and posterior tibial pulses absent on left with retarded vein filling	Left lumbar sympathectomy, L_1, L_2, L_3	Early relief of claudication and reversal of color changes; return of claudication after 3 mo.; area of sweating noted about the inner aspect of left knee; has never ceased smoking completely
XIX	A. Z.	38	Bilateral claudication and swelling; color changes and ulceration of left foot	3 yr.	Gangrene of the tips of the 4th and 5th toes left foot; absent posterior tibial and dorsalis pedis pulses bilaterally; marked color changes and hyperhidrosis; left calf 2 cm. less in diameter than right	Bilateral lumbar sympathectomy, L_2, L_3, L_4	Prompt reversal of color changes and progressive loss of claudication; feet warm and dry; no change in pulsations; asymptomatic; not smoking

excellent progress noted initially after operation:

CASE XVIII. Nathan W., a thirty-four year old white male, had received a medical discharge from the U. S. Navy in July, 1945 because of phlebitis. He had been treated with paravertebral sympathetic block and ligation of the left saphenous vein. Upon discharge from the Navy he noted that he had severe cramping pain in the left calf after walking two or three blocks, and the physician whom he consulted suggested the diagnosis of thromboangiitis obliterans and advised him to cease smoking. Upon admission to this clinic positive physical findings were limited to the peripheral vascular system. Both lower extremities, especially the feet, were noted to be cool and hyperhidrotic. Moderate color changes were noted in the left foot on elevation and depression. The posterior tibial and dorsalis pedis arteries were impalpable on the left and the lower extremities exhibited decreased oscillometric readings. Vein filling in the left foot was noticeably retarded. Since paravertebral blocks, L_1 to L_3, caused the left foot to become warm, dry and pink, with diminution of claudication time and since the usual medical therapy over a period of two months resulted in no clinical improvement, the patient was subjected to left lumbar sympathectomy. (Table I.) Immediate results were good. The patient was ambulatory after the fifth day and was gratified to note the progressive decrease in calf claudication and reversal of color changes. Although he professed to have stopped smoking, at no time did he cease for more than two or three days. Three weeks after operation he again began to complain of the left calf and an area of sweating was noted about the left knee.

This case illustrates two facts which may detract from the otherwise good results of sympathectomy: One, of course, is the continued use of tobacco and the other is evidence of incomplete sympathectomy. However, it is our impression that the latter contributes little to the recurrences of this patient's symptoms.

That the superficial circulation in an extremity is enhanced after sympathectomy has been shown in excellent plethysmographic studies by Abramson,[15] among others. However, it is not correct to infer from such studies, as some have done, that augmentation of the superficial circulation occurs at the expense of the deep blood flow after sympathectomy. In fact, Goetz[16] using his exquisite digital plethysmographic technic, has recorded changes in his patients indicating increase in deep blood flow after sympathectomy. Of his twenty-nine patients followed one to eleven years after operation, none showed any decrease in augmented blood flow achieved by sympathectomy. Using forearm plethysmography with certain ingenious auxiliary technics, Barcroft and Edholm[10] in a recent report have concluded that blood flow in muscles of normal individuals is more than doubled by the release of sympathetic tone. In addition they reported that vasoconstrictor tone may gradually return to the blood vessels of sympathectomized subjects. The latter observation is contrary to the experiences of Goetz and not in evidence in our own patients at this time. It may be that Barcroft and Edholm are referring to the return of local vasomotor tone and not that mediated through sympathetic fibers.* In this latter opinion we concur. It has been our impression that the majority of patients suffering from thromboangiitis obliterans characteristically have high vascular tone. Protection of the young collateral circulation from vasoconstricting influences is of prime importance in the acute phase of this disease, and a permanent protecting influence is obtained by interruption of the sympathetic pathways.

As a rule the psychosomatic aspects of thromboangiitis obliterans have been given little attention in previous studies. Since this disease engenders so much economic debility with prolonged medical treatment, it is not remarkable that these patients often present a negative attitude and are inclined to be anxious and tense. That these functional expressions in turn may influence the speed of recovery and may initiate vasoconstricting stimuli to the extremities is

* In a personal communication Professor Barcroft has clarified this point by stating that he refers to return of local vasomotor tone.

not beyond our comprehension of the integration of functional and organic disease. The effect of a chain of constrictor impulses, such as just mentioned, on the blood supply to a digit has recently been demonstrated by Goetz[16] in digital plethysmographic studies. Weiss[17] has reported on a case of psychogenic peripheral vasospasm simulating organic vascular disease and he was able to obtain complete reversal of symptomatology in his patient by appropriate psychotherapy. It is of interest to speculate on the course of the disease in Weiss's patient if he had not proven to be amenable to psychotherapy. To us, therefore, interruption of the pathways carrying vasoconstricting impulses appears to be a good prophylactic measure in thromboangiitis obliterans when high vasoconstrictor tone is demonstrated. Since few reports previously written on this subject have contained a careful re-evaluation of patients at the end of two years, this series of cases with such favorable early and late results is submitted to substantiate this statement.

SUMMARY

1. The methods of study, distribution of patients and results of sympathectomy in nineteen cases of thromboangiitis obliterans are discussed.

2. Evidence supporting the view that sympathectomy increases deep blood flow to an extremity is reviewed.

CONCLUSION

Sympathectomy in properly selected cases of thromboangiitis obliterans causes early relief of symptoms as well as rapid rehabilitation of the patient, as noted in our two-year re-evaluation and follow-up. No deleterious effects resulting from this operation have been noted in this series. The disturbances in sexual function that may arise because of the operative procedure have been discussed.

REFERENCES

1. Goodman, E. N., Messinger, W. J. and White, J. C. Indications and results of surgery of the autonomic nervous system in naval personnel. *Ann. Surg.*, 124: 204, 1946.
2. Lyons, R. H., Moe, G. K., Neligh, R. B., Hoobler, S. W., Campbell, K. N., Berry, R. L. and Rennick, B. R. The effects of blockage of the autonomic ganglia in man with tetraethylammonium. *Am. J. M. Sc.*, 213: 315, 1947.
3. Hitzrot, L. H., Naide, M. and Landis, E. M. Intermittent claudication studied by a graphic method. *Am. Heart J.*, 11: 513, 1936.
4. Naide, M., Sayen, A. and Comroe, B. I. Characteristic vascular pattern in patients with rheumatoid arthritis. *Arch. Int. Med.*, 76: 139, 1945.
5. Freeman, N. E. The diagnosis and treatment of thrombo-angiitis obliterans in the vascular centers of Army General Hospitals. *Am. Heart J.*, 33: 332, 1947.
6. White, J. C. and Smithwick, R. H. The Autonomic Nervous System, 2nd ed. The Macmillan Co., New York, 1941.
7. Silbert, S. Treatment of thrombo-angiitis obliterans, *Hebrew M. J.*, 1: 3–11, 1942.
8. Friedlander, M., Silbert, S., Bierman, W. and Laskey, N. Differences in temperature of skin and muscles of the lower extremities following various procedures. *Proc. Soc. Exper. Biol. & Med.*, 38: 150, 1938.
9. Wilkins, R. W. Sympathetic Nervous Control of the Peripheral Vascular System, Advances in Internal Medicine. Vol. 1. New York, 1942. Interscience Publishers, Inc.
10. Barcroft, H. and Edholm, O. G. Sympathetic control of blood vessels of human skeletal muscle. *Lancet*, 15: 513, 1946.
11. Harris, R. I. The role of sympathectomy in the treatment of peripheral vascular disease. *Brit. J. Surg.*, 23: 414, 1935.
12. Freeman, N. E. and Montgomery, M. Lumbar sympathectomy in the treatment of intermittent claudication: selection of cases by claudication test with lumbar paravertebral procaine injection. *Am. Heart J.*, 23: 224, 1942.
13. Leriche, R. and Fontaine R. Einige Bemerkungen über 1199 Operationen am Sympathikus. *Arch. f. klin. Chir.*, 186: 338, 196.
14. deTakats, G. The value of sympathectomy in the treatment of Buerger's disease. *Surg., Gynec. & Obst.*, 79: 359, 1944.
15. Abramson, D. I. Vascular Responses in the Extremities of Man in Health and Disease. Chicago, 1944. Univ. Chicago Press.
16. Goetz, R. H. The rate and control of the blood flow through the skin of the lower extremities. *Am. Heart J.*, 31: 146, 1946.
17. Weiss, E. J. Psychogenic peripheral vasospasm. *Psychosom. Med.*, 8: 274, 1946.

Consideration of Glomerular Nephritis in Its Relation to Sulfonamide Sensitivity*

R. H. RIGDON, M.D., W. H. SIDDON, M.D. *and* D. E. FLETCHER, PH.D.

Galveston, Texas *Little Rock, Arkansas*

ALTHOUGH the etiology in every case of glomerular nephritis may not be established, it is widely accepted today that there is some relationship between steptococcus infections and glomerular nephritis. A non-suppurative type of inflammatory reaction occurs within the kidney which according to Forbus[1] "is probably always secondary to some other pathological processes even though the primary affection may be so hidden as to remain undiscovered." The experimental studies of Longcope and his associates[2,3] and Long and Finner[4] suggest that the renal lesion results from a process of sensitization, or an allergic type of reaction.

Experimental and clinical studies by many investigators have emphasized that sensitivity to sulfa drugs frequently occurs in man. The pathologic lesions that constitute this reaction indicate that it may occur in a variety of tissues, among which may be mentioned skin, blood vessels, heart, kidneys, liver, spleen and lungs.[5–9] The similarity of this reaction to the sensitivity reaction produced by horse serum and certain chemical compounds has been pointed out.[5,10–12]

The specific nature of antigenic substances is now well recognized and this characteristic depends upon their chemical composition. Immunologically active antigens may be produced by conjugating pure chemicals with animal serum proteins or other proteins. The specificity of the antigen depends upon the chemical radical and not upon the protein of the conjugated antigen.[12,13] It has been shown that following development of sensitization by repeated contact with certain chemicals, anaphylaxis may occur following further contact.[14,15]

The question arises, in this problem of sensitization, whether there is experimental or clinical evidence to indicate that if the serum of one person conjugates with a compound to form an antigenic substance, is it more likely that the serum of this same person will conjugate more readily with another compound to form a second antigenic substance than will the serum of an individual who failed to conjugate with the first compound to form an antigenic substance? In other words, is there evidence to indicate that an individual is more likely to become hypersensitive to a second antigen than a person who never showed any sensitization reactions?

Rackemann[16] in 1945 asked the questions "What is the allergic individual? Why is it that only a few persons become clinically sensitive? How many patients who suffer from eczema in childhood develop other manifestations of allergy: hay fever in their teens, asthma in their twenties, or possibly migraine later on? Are those the same individuals who as they grow older manifest reactions to penicillin, to the sulfonamide or perhaps get into trouble with dermatitis or industrial asthma? In other words, must we not regard the 'asthmatic state' as dependent upon a physiologic change and regard the 'allergic individual' as having something about him which is basic and fundamental and which last all through life."

Although hypersensitivity to a single

* From the Departments of Pathology and Medicine, University of Arkansas School of Medicine, Little Rock, Ark.

antigen is the rule, we sometimes see a patient who is sensitive to more than one antigen. More and associates[7] reported a case (No. 18) in which sulfathiazole "appeared to induce asthmatic attacks" in a patient who gave a history of asthma. Rackemann and Green[17] have observed eight cases of periarteritis nodosa associated with bronchial asthma and found a history of asthma in 8 per cent of 229 cases of periarteritis nodosa reported in the literature. Riemann and associates[18] observed periarteritis nodosa in two patients who had trichinosis and they suggested a relationship with the high degree of sensitivity that develops to the trichina antigen. Individuals supposedly sensitive to horse serum may react quite differently when small amounts of the same form of antisera derived from different animal species are injected intramedially.[19] Nelson[20] observed that in a patient sensitized to sulfathiazole an acute febrile reaction may occur following administration of sulfadiazine and sulfapyridine. Rich[8,9] in his studies on periarteritis nodosa described eight cases in which this lesion was found at autopsy in patients who had hypersensitive reactions resulting from foreign serum and sulfonamide therapy. Rich[8] stated "that widely different sensitizing antigens can be responsible for the development of the vascular lesions in different patients. It is not improbable that bacterial antigens may be concerned in some cases." Should one consider it merely a coincidence that of five of Rich's patients who shortly before death had sensitivity reactions following therapeutic injections of foreign serum, four also had received sulfonamides?

Any hypothesis as to the relationship of glomerular nephritis associated with a streptococcus infection and sulfa sensitivity may be difficult to establish either clinically or pathologically. However, a recent pathologic study of three cases has emphasized the need to consider such a hypothesis. These cases also indicate the necessity for caution in use of the sulfa drugs when there is a history of sensitivity to any antigen. In two of these three subjects streptococci were isolated from the blood and cocci were demonstrated on the heart valves. Both patients had a progressive type of intracapillary glomerular nephritis. The third patient gave a history of "flu" and swelling of many joints, petechiae, nausea, vomiting and severe anemia. Typical lesions of glomerular nephritis were present. In each of these three cases there were pathologic lesions similar to those resulting from hypersensitivity to sulfa drugs.

CASE REPORTS

CASE 1. The patient, a white female aged thirty-five years, was admitted to the University Hospital with the chief complaint of stiffness and pain in the joints "for four months." This illness began with flu and involvement of the joints followed within a month. The right hip became stiff and soon thereafter all extremities were involved. The fingers were stiff and numb. The tendons along the dorsum of the hands and feet were painful and red streaks developed along these surfaces. The pain was severe enough to make the patient "feel like screaming."

The patient thinks there was a little fever at times. She had epistaxis and spat up blood on several occasions. There was some shortness of breath and "smothering spells" following exertion. The heart was noted to beat fast at times and a sensation of "flutter" was observed over the precordium.

Approximately two months following onset of symptoms the patient said she was given "sulfa" for the "flu." She developed nausea, vomiting, rash and dizziness following this course of therapy. Approximately one month later she developed an "awful cutting pain" in the chest. A sulfa drug was given the following day. Nausea and vomiting occurred. Only six tablets were taken. Ten days later she developed itching of her fingers and feet. A rash developed on the hands, arms and lower extremities, which persisted for forty-eight hours. A few small nodules were observed by the patient on the skin about the elbows. These would appear and disappear according to the history.

The patient said that she had been anemic since she was sixteen. An appendectomy was performed when she was twenty-five. Tonsillitis occurred during childhood; there was no history of rheumatic fever. There were two miscarriages

before she delivered a live child. A second baby was born eight months preceding onset of her present illness. There was a history of arthritis in two of her sisters whose ages were not given. There was no history of sensitivity in this patient.

Upon physical examination the patient was observed to be apathetic and appeared ill. Pain occurred upon movement of the extremities. There was neither swelling nor an increase in temperature of the joints. The heart was normal in size and the sounds were distant and weak. Nothing abnormal was noted during examination of the chest. The temperature was 97.8°F., pulse, 84 per minute and respiration, 20 per minute. The systolic pressure was 115 mm. of Hg and diastolic was 75 mm. Hg.

The specific gravity of four specimens of urine varied between 1.009 and 1.010. A few white blood cells and 6 to 15 red cells per high power field were present. Only a trace of albumin was found. The non-protein nitrogen was 200 mg. per cent four days preceding death. The total plasma protein at this time was 6.5 Gm. per cent with the A/G ratio 1.38. The creatinine was 4.7 mg. per cent. The day preceding death the non-protein nitrogen was 225 mg. per cent, creatinine 5.3 mg. per cent and blood sodium chloride 430 mg. per cent. The phenolsulfonphthalein test was negative for dye in all samples.

The patient was anemic on admission and two days later the red cell count was 1.51 million, hemoglobin 4.2 Gm. and the hematocrit reading was 14 per cent packed cells. Color index was 0.93 and the volume index 1.16. The white blood cell count was 18,050 and platelet count was 51,340. The reticulocyte count was 1.3 per cent while the icteric index was 5.6. Coagulation and retraction times were normal.

A sternal bone marrow aspiration biopsy showed general hyperplasia. Cells of the erythrocytic series were prominent, constituting about 30 per cent of the total nucleated forms. Polychromatophilic erythroblasts were conspicuous by their presence. Several megakariocytes were present. Several mitotic figures were seen which probably also indicate a hyperplastic state of the tissue. These findings apparently do not fit into any definite pattern. The anemia was practically normocytic and normochromic. It was suggested that "the bone marrow was acted upon by some active depressant which was responsible for the anemia, and our studies were made at a time when the hematopoietic tissue was in violent, but ineffective, efforts of regeneration."

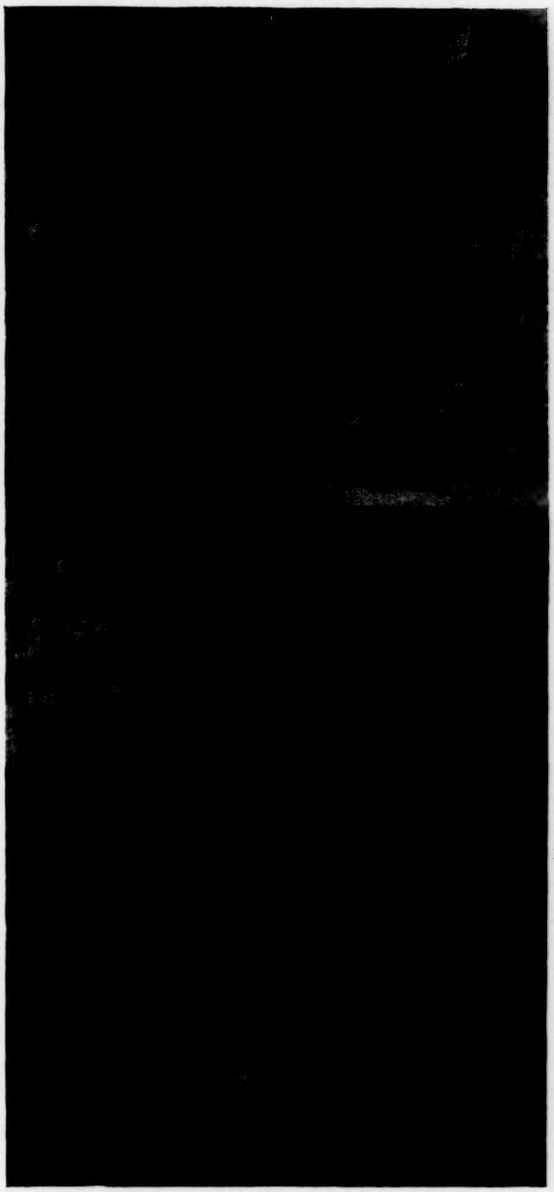


FIG. 1. Case I. A, there is an increase in the number of cells infiltrating the mitral valve. Sometimes these cells are in small groups adjacent to the endocardial surface. B, the cells present in the mitral valve are usually mononuclear; however, few polymorphonuclear leukocytes are present. No bacteria are present; hematoxylin and eosin stain.

The patient remained in the hospital for eleven days during which time the joint pain persisted. The temperature was not elevated. She was given transfusions of whole blood on

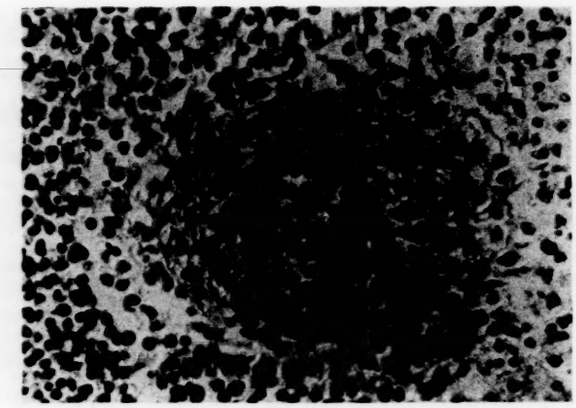


FIG. 2. Case I. The walls of many of the blood vessels within the spleen are edematous and fragmented. Portions of the vessel wall stain deeply with eosin. Some of the vessel walls have mononuclear and polymorphonuclear cells infiltrating them; hematoxylin and eosin stain.

several occasions and frequently reacted to them with slight chills and an elevated temperature.

Pathologic examination revealed that the skin had a pale yellow color. Several petechiae were present in the skin over the buttocks. The serous cavities were filled with straw colored fluid, 1,000 cc. in the abdominal, 1,000 cc. in the right and 500 cc. in the left pleural cavity and 30 cc. in the pericardial sac.

The heart weighed 300 Gm. A fine granular exudate covered the visceral layer of pericardium. A few petechiae were present in the endocardium, myocardium and pericardium. The right ventricle was moderately dilated. No gross lesions were observed in the endocardium although microscopically the mitral valve was infiltrated with a moderate number of mononuclear cells and a few polymorphonuclear leukocytes. (Fig. 1.) Small areas of fibrinoid-like tissue were present within the valve.

The lungs were edematous and there were many areas of bronchopneumonia and also focal areas of fibrosis within the alveoli. There were areas of hemorrhage within the lung tissue. The liver weighed 1,850 Gm. The hepatic cells were swollen and there were small focal areas of fat within the liver tissue.

The spleen weighed 230 Gm. There was an apparent increase in the number of mononuclear cells within the pulp. The walls of some of the smaller blood vessels were fragmented and fibrinoid tissue was present. Mononuclear cells and polymorphonuclear leukocytes infiltrated these vessel walls and the adjacent stroma. Sometimes this degenerative process appeared

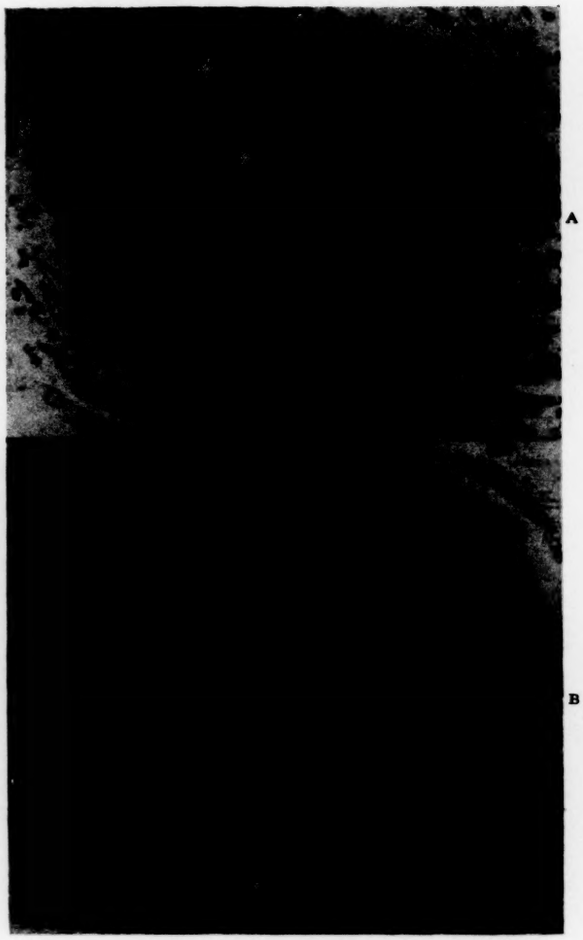


FIG. 3. Case I. A, there is a proliferation of cells within the tuft and many have polymorphonuclear leukocytes in the tuft and in Bowman's space. Within many of the tufts are masses of a deep, eosin-staining material. Some of the glomeruli have many polymorphonuclear leukocytes and mononuclear cells infiltrating the wall and surrounding the entering arteriole; hematoxylin and eosin stain. B, some of the glomeruli are partially fibrotic while others are completely fibrotic; hematoxylin and eosin stain.

to involve the fibrous septa in the spleen. (Fig. 2.)

There were several small ulcerated areas in the mucosa of the cecum and colon. The degenerative and inflammatory reaction extended down into the submucosa.

The combined weight of the kidneys was 390 Gm. There were many petechiae in the cortex and also focal areas which appeared slightly yellow in color. Many of the glomeruli were completely fibrosed while others were partially scarred. (Fig. 3.) There was an increase in the cellular elements of the remaining tufts such as that observed in intracapillary glomeru-

lar nephritis. A few of the glomeruli showed a large number of mononuclear and polymorphonuclear leukocytes within the tuft. The wall of an occasional entering arteriole was infiltrated by similar cells. (Fig. 3A.) Red blood cells and leukocytes were present in Bowman's space and they filled the lumen of many tubules. Albuminous casts were present in the lumen of the tubules; the epithelial cells lining the convoluted portion of the tubules usually were low and stained deeply with hematoxylin. There were a moderate number of mononuclear cells infiltrating the stroma between the renal tubules.

Anatomic Diagnosis: (History of sulfa therapy on two occasions with symptoms of hypersensitivity); periarteritis nodosa involving the arteries in the spleen; petechiae in endocardium, myocardium and pericardium; chronic inflammatory reaction in mitral valve; acute and chronic intracapillary glomerular nephritis; acute pericarditis and acute ulcerations in area of cecum. (History of uremia); moderate dilatation of right ventricle; ascites, 1,000 cc.; hydrothorax, left 500 cc. and right 1,000 cc.; splenomegaly; ecchymosis of the left buttock; bronchopneumonia; focal areas of chronic pneumonia.

Comment: As far as is known this woman was in perfect health until she developed a pulmonary infection approximately four months preceding death. Subsequent to the first infection pain and swelling of the joints occurred. Sulfa was given on two occasions. Nausea, vomiting and petechiae of the skin occurred following the second course of therapy. When she entered the University Hospital eleven days before death, there was severe anemia and laboratory findings indicative of renal failure.

The inflammatory reaction involving the mitral valve certainly suggests an early acute rheumatic process. Necrosis and cellular reaction in the septa of the spleen are similar to the lesions described by More and associates[7] in patients showing sulfa sensitivity. Glomerular lesions, inflammatory reaction on the mitral valve and necrosis in the spleen, each suggest a hypersensitive reaction. The renal lesions according to the patients history developed within a period of four months. Usually hypertrophy of the left ventricle and hypertension occur in patients who live to be thirty-five years of age before developing renal insufficiency when the nephritic process begins in childhood. The majority of glomeruli showed the typical lesions of glomerular nephritis. The few glomeruli that showed a fibrinoid material and an infiltration of leukocytes and mononuclear cells within the tuft reminded us of the similarity of this renal lesion to the vascular lesions in the spleen.

Clinically, there was nothing to suggest a bacterial infection in this patient and furthermore nothing was found at autopsy to indicate an infection. Active glomerular lesions do occur in cases of chronic glomerular nephritis; however, it is suggested that in this patient some of the glomerular lesions may have been a part of the hypersensitive reaction to the sulfa drugs. The mitral lesion at this time was more likely that of acute rheumatic fever; however, it is significant to find this variety of hypersensitive reactions in one individual. Recently one of us (R. H. R.) saw a case of sulfa sensitivity in a white female approximately sixty-five years of age. Acute arthritis with subsequent myocardial damage followed the skin manifestation of hypersensitivity within a period of two weeks.

CASE II. The patient, a thirty-nine year old white male, was admitted to the University Hospital with a history of high fever and pain in the chest three weeks preceding time of death. Onset of this illness was two months previously at which time he became nauseated and vomited while at work. That night he thought that he had some fever. He was unable to work for a week; however, he returned to work the second week although he was weak and lethargic. He had fever during this period. A month following onset of illness he was hospitalized and roentgenologic examination of the chest showed changes interpreted as "suspicious lesions that should be carefully watched." The temperature was high and it spiked daily. There was an increase in the degree of shortness of breath. The patient noticed that his urine was blood-tinged.

On admission the patient was acutely ill. The temperature was 102.4°F., pulse 130 per minute, respiration 26 per minute and the systolic blood pressure 130 mm. Hg and the diastolic pressure 80 mm. Hg. The skin was hot, moist and pale. Respirations were chiefly abdominal in type. There was dullness over the right lower lobe and fine moist râles were present over both lungs.

The urine contained a 2 to 4 plus albumin and two days before death many red blood cells were present. The non-protein nitrogen was 100 mg. per cent three days preceding death. At this time the creatinine was 2.3 mg. per cent, plasma proteins 8.36 Gm. per cent, albumin 3.09 Gm. per cent, globulin 5.27 Gm. per cent and the A/G ratio was 0.59. On admission there was anemia with only 2.62 million red blood cells and a hemoglobin of 58 per cent. The white blood cell count was 8,850. Both the red and white cell counts remained low in spite of several transfusions of whole blood. A non-hemolytic streptococcus was isolated from the blood stream ten days preceding death and a second positive culture was obtained a few days after the first.

During the period of hospitalization a coarse presystolic and systolic murmur developed over the mitral area. Dilatation of the right and left ventricle subsequently occurred, accompanied by pulmonary and peripheral edema. Classical signs of right pleural effusion developed. Death followed an episode of acute respiratory difficulty.

The patient, while in the University Hospital, was treated with large doses of penicillin. Sulfadiazine was given only twice on the seventeenth day preceding death. No clinical reactions to the sulfa were noted. The patient had received sulfathiazole, however, approximately seventy days previously for a period of eight days.

Pathologic examination revealed the following: There was a small amount of edema of the lower extremities; 1,000 cc. of straw colored fluid was present in the peritoneal cavity and 800 cc. of a slightly turbid fluid was present in the right pleural cavity.

The heart was large as a result of dilatation of both the right and left ventricles. The myocardium was pale and flabby. Multiple polypoid vegetations arose from the auricular surface of the tricuspid valve; some of these were 2.0 cm. in diameter; they were soft and friable. There was nothing on the tricuspid valve or the other valves of the heart to suggest a lesion older than the acute endocarditis. Innumerable gram-positive cocci were embedded in the necrotic tissue of the valve.

The right lung was atelectatic as a result of the presence of fluid in the cavity. Multiple infarcts were present in both lungs, these varied both in age and in size. Many of the branches of the pulmonary artery were occluded by infected emboli.

The liver weighed 2,175 Gm. and showed the typical changes of chronic passive congestion. The spleen weighed 530 Gm.; it was soft in consistency. A few petechiae were present in the mucosa of the gastrointestinal tract. Histologically, the wall of several of the small arteries in the submucosa appeared coagulated and they were surrounded by a collection of inflammatory cells, mostly of the mononuclear variety. (Fig. 4A.)

The kidneys together weighed 515 Gm. Many petechiae were present in the cortex. There were small focal yellow areas throughout the cortex which represented tubular degeneration. The lumen of many of the tubules and some of the tufts were filled with red blood cells. There was a marked increase in the number of cells in the glomeruli which apparently were endothelial cells. Few leukocytes and mononuclear cells also were present in some of the glomeruli. An occasional glomerulus had either a fibrous adhesion or a proliferation of epithelial cells between its tufts and capsule. There was some edema of the interstitial tissue of the kidney and a moderate number of mononuclear cells were present. An occasional eosinophile was present in the interstitial tissue.

Anatomic Diagnosis: (History of acute bacterial endocarditis due to a non-hemolytic streptococcus); acute bacterial endocarditis involving the tricuspid valve; dilatation of cavities of the heart; emboli in branches of pulmonary artery; multiple infected infarcts in both lungs; chronic passive congestion of viscera; ascites 1,000 cc. pleural effusion, right 800 cc.; atelectasis of right lungs; edema of lower extremities; acute splenic tumor; acute and subacute intracapillary glomerular nephritis; periarteritis nodosa involving arteries in colon; (history of sulfa therapy); atrophy of testicle; healed pulmonary tuberculosis; fibrous pleural adhesions.

Comment: The patient was sick for approximately three months with elevated

temperature and dyspnea. When admitted to the University Hospital three weeks preceding time of death, a non-hemolytic streptococcus was isolated from the blood on two occasions. There was severe anemia at this time and retention of non-protein nitrogen. The urine showed 2 plus albumin.

The pathologic changes on the tricuspid valve were typical of acute bacterial endocarditis. There was no evidence in this heart of an old rheumatic process; furthermore, there was no history of such an infection. The kidneys were typical of the so-called intracapillary type of glomerular nephritis. The process was active as indicated by the presence of red blood cells within the lumen of many of the tubules. There were no embolic phenomena observed in any of the viscera except the lungs. Apparently all of the infected emboli were filtered out by the lungs.

The lesions in the blood vessels of the colon were identical with those of periarteritis nodosa as described by Rich.[8,9] No other pathologic changes were observed in the blood vessels to indicate a sensitivity reaction. The last dose of sulfa this patient received was sulfadiazine seventeen days before death. It would seem more likely that the intracapillary glomerular nephritis was associated with the streptococcus infection rather than with the sulfa therapy.

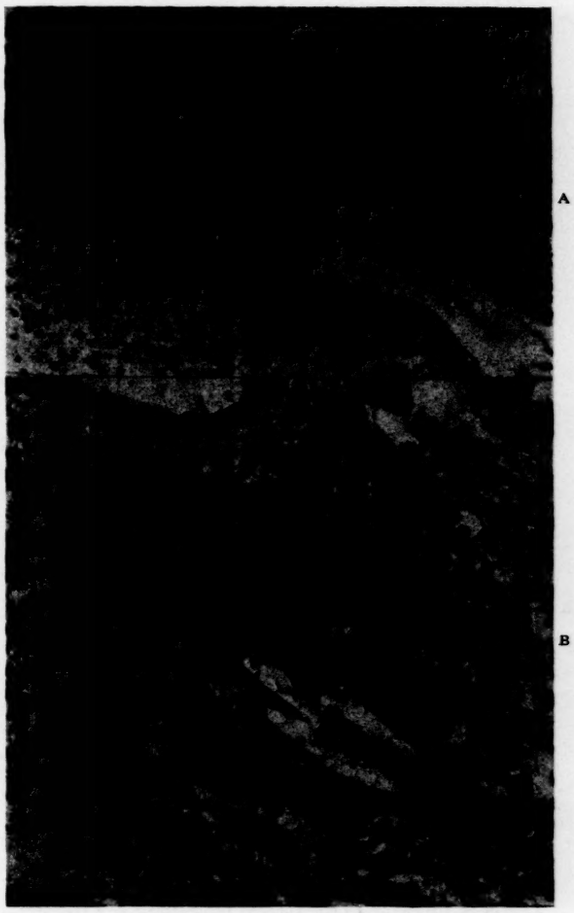


FIG. 4. A, this illustrates the typical periarteritis nodosa lesion which is present in the colon. No bacteria were demonstrated in this lesion; hematoxylin and eosin stain (Case II). B, a portion of the wall of this vessel in the kidney is necrotic. The vessel wall and the surrounding tissues are infiltrated with mononuclear cells; hematoxylin and eosin stain (Case III).

CASE III. The patient, a white female aged seventeen, was admitted to the University Hospital with a history of hematuria, nausea and vomiting and during the previous two days there were periods during which she was irrational. Ten weeks previously she stuck a nail into her foot. Home remedies were used for two weeks at which time she consulted a physician who gave her sulfa. The infection in her foot improved; however, she developed a cold and sore throat which necessitated bed rest. During this time there was a backache and headache.

Two weeks prior to the time of hospitalization she developed another cold, sore throat and fever. She was given two tablets of sulfa every four hours for twelve days. Nausea and vomiting began before this course of therapy was completed. Two days before admission the urine was thought to contain blood and a few petechiae appeared in the skin over the breast. Two years previously an illness occurred characterized by hematuria, headaches and lumbar pain. Since this time, edema of the face had been observed in the mornings.

On physical examination the systolic blood pressure was found to be 142 mm. Hg and the diastolic 90 mm. Hg, the pulse 92 per minute, respiration 24 per minute and the temperature 100°F. Her face was edematous and she appeared anemic and acutely ill. Petechiae were present over the breast. Numerous small "moth eaten" areas were present in the retina. The nasal mucosa was ulcerated bilaterally. The heart was normal in size and a harsh systolic murmur could be heard over the entire precordium; it was loudest at the apex.

FIG. 5. Case III. A, Bowman's space and the lumen of many of the tubules are filled with red blood cells. The cells lining the convoluted portion of the tubules are cuboidal and stain deeply with hematoxylin. Collections of mononuclear cells, among which are eosinophiles, are present in the interstitial tissue; hematoxylin and eosin stain. B, the glomeruli show a marked proliferation of cells within the tuft. Essentially all the glomeruli are like this one; hematoxylin and eosin stain.

During the ten days of hospitalization the specific gravity of the urine varied between 1.010 and 1.020. There usually were 12 to 20 red blood cells and 3 to 5 white blood cells per high power field. Red blood cell count on admission was only 2.44 million and hemoglobin was 68 per cent. White blood cell count was 16,550 with 82 per cent polymorphonuclear leukocytes, 1 per cent stabs, 14 per cent lymphocytes and 3 per cent monocytes. The white blood cell count varied very little during the period of hospitalization. The red cell count increased following transfusions. On admission non-protein nitrogen was 168 mg. per cent and two days before death it was 167 mg. per cent, albumin 3.59 Gm. per cent, globulin 2.57 Gm. per cent, A/G ratio 1.40 and total protein 6.16 Gm. per cent. On the day preceding death creatinine was 3.53 per cent, blood sodium chloride 402 mg. per cent and carbon dioxide combining power 64 volumes per cent.

Three transfusions of whole blood and 20,000 units of penicillin every three hours were given during the ten days that she remained in the hospital. A pericardial friction rub was observed the day preceding death and on the day of death the urine was grossly bloody.

Pathologic study revealed the following: A few petechiae were present in the skin and there was some edema of the lower extremities. Straw colored fluid was present in the serous cavities, 2,000 cc. in the peritoneal cavity, 200 cc. on each side of the thoracic cavity and 100 cc. in the pericardial cavity.

The heart was normal in weight and the cavities were dilated; the musculature was pale and flabby. There was an area of acute reaction over the surface of the right atrium. Large friable vegetations were present on the leaflets of the pulmonary valve. The infection had extended to the adjacent endocardium and into the pulmonary artery. Gram-positive cocci were present in the necrotic vegetations. Cultures were positive for streptococcus viridans.

The lumens of many of the branches of the pulmonary artery were filled with infected emboli. Many infarcts were present in both lungs, these varied both in age and in size.

The liver extended 4 fingerbreadths below the right costal margin and showed the changes typical of chronic passive congestion. The spleen weighed 765 Gm. and it was soft in consistency. Small groups of hematopoietic cells were present in the pulp. A few petechiae and a few superficial ulcerations were present in the mucosa of the colon.

The kidneys together weighed 1,000 Gm. They were pale and edematous. Focal areas of tubular degeneration and small hemorrhages were present in the cortex. The lumen of many of the tubules were filled with red blood cells, casts and albumin. (Fig. 5A) All the glomerular tufts showed a marked increase in the number of endothelial-like cells. (Fig. 5B). An occasional fibrous adhesion was present between the tuft and Bowman's capsule. The renal interstitial tissue was edematous and diffusely infiltrated with mononuclear cells, some of which were eosinophilic. The walls of some of the small blood vessels in the kidneys were edematous, fragmented and necrotic. Mononuclear cells infiltrated the wall of such vessels and extended out into the surrounding tissue (Fig. 4B.)

Anatomic Diagnosis: (History of nail wound of foot four months previous to death; sulfa therapy with hypersensitive reaction; nephritis with uremia); acute bacterial endocarditis involving pulmonary valve with extension to adjacent endocardium and into the pulmonary artery (streptococcus viridans); localized area of acute pericarditis over right auricle; multiple infected emboli in branches of pulmonary artery; multiple infarcts in both lungs which vary widely in size and age; dilatation of right ventricle; ascites 2,000 cc.; hydrothorax, bilateral 200 cc.; hydropericardium 100 cc.; splenomegaly (765 Gm.); acute and subacute intracapillary glomerular nephritis; acute ulcerative colitis (uremic); periarteritis nodosa in renal vessels with mononuclear infiltration of interstitial tissue of the kidneys; (hypersensitive reaction of sulfa); petechiae in skin and viscera; generalized lymphadenitis of superficial lymph nodes; chronic cystitis; chronic cervicitis.

Comments: This girl apparently developed a streptococcus infection of the pulmonary valve as the result of the nail wound which occurred three months before death. She was treated with sulfa drugs on two occasions during this interval. No reaction occurred following the first course of sulfa therapy; however, when it was repeated approximately six weeks later, nausea, vomiting and petechiae occurred.

On admission to the University Hospital nine days preceding the time of death the clinical and laboratory findings were consistent with the diagnosis of nephritis accompanied by uremia. The pathologic lesions were typical of acute bacterial endocarditis involving the pulmonary valve. There was nothing to suggest either a previous injury to this valve or malformation. The renal lesion was that of intracapillary glomerular nephritis. The presence of red blood cells in the lumen of many of the tubules would indicate an active process. An interstitial reaction certainly occurs in both acute and subacute glomerular nephritis as observed in the cases of nephritis associated with scarlet fever. The significant feature, however, of the interstitial reaction in this patient is the presence of eosinophilic mononuclear cells. There were many groups of mononuclear cells in the interstitial tissue. Such a reaction has been described by Lichtenstein and Fox,[5] French[6] and More and associates[7] in cases of sulfa hypersensitivity. The presence of periarteritis nodosa-like lesions in the interstitial tissue of the kidneys apparently supports the rôle that sulfa sensitivity may have played in this case.

Glomerular and tubular lesions such as we have in this patient are similar to those accompanying streptococcus infection and are thought to be the result of sensitivity to this organism. The presence of periarteritis nodosa-like lesions in the interstitial tissue is indicative of a sensitivity reaction and in view of the frequency in which this lesion occurs following sulfa drugs it is suggested that in this case it is the result of the sulfa.

This case is of interest also from the standpoint of the infrequency of streptococcus infections involving the pulmonary valve. In four of the five cases cited by Rogers endocarditis was acute.[21] Allen[22] expressed the opinion that virulent organisms are more likely to produce acute lesions on the right side of the heart than avirulent ones. Streptococcus viridans usually produces a subacute type of endocarditis; however, Held and Goldbloom[23] have observed cases in which they considered the lesion to be produced by streptococcus viridans and considered it to be acute.

COMMENTS

Our interest in glomerular nephritis and sulfa sensitivity resulted from the observation that a majority of our patients showing hypersensitivity reactions, as observed at autopsy, also had glomerular nephritis. The total number of such cases, of course, is small; however, it will be of interest to determine if such a combination of lesions is merely a coincidental finding in these three patients.

As a result of both experimental and clinical observations it is now widely accepted that hypersensitivity to the streptococcus may manifest itself as glomerular nephritis, and hypersensitivity to sulfa drugs may manifest itself as an interstitial

renal lesion and periarteritis nodosa. The experimental studies of Rich and Gregory[24] emphasize this problem of sulfa sensitivity and glomerular nephritis. Three of five rabbits given both horse serum and sulfadiazine developed acute glomerular nephritis. The similarity of the renal changes in these rabbits to the glomerular lesions observed in our three patients is obvious from their description: "There was condensation of glomerular tufts with syncytial proliferation of the glomerular epithelium, hemorrhage in Bowman's capsule and in the tubules and albumin and casts in the tubules . . . The attack was upon the glomeruli independent of the arterioles." Hemorrhage in Bowman's space and blood within the tubules were found frequently in our three human cases. In commenting upon the experimental renal lesions, Rich and Gregory[24] say that "the glomerular lesions in our rabbits are of the same nature as the fresh glomerular lesions described by Longcope and attributed by him to anaphylactic hypersensitivity."

The same type of sensitivity reaction in blood vessels may occur following administration of horse serum, sulfa drugs and certain chemical compounds.[10,12] In our first case it is interesting to observe the type of reaction within the glomeruli and that in the wall of the blood vessels in the spleen and in the mitral valve. In each of these three sites mononuclear and polymorphonuclear cells were present and also there were small focal areas of deep eosin-staining fibrinoid-like tissue. Our attention would not have been attracted to this glomerular change if there had not been both a clinical history of sulfa sensitivity and pathologic lesions elsewhere in the body consistent with hypersensitivity. The pathologic changes in the mitral valve would suggest an acute rheumatic lesion. However, Clark and Kaplan[25] observed a similar inflammatory process in the valves of a patient who died as the result of serum sickness. It is widely accepted at this time that acute rheumatic fever is the result of a hypersensitivity reaction. It is suggested that a similar lesion may occur in the valves of the heart as a result of sulfa sensitivity, as has been described by Leary[26] in acute rheumatic endocarditis and Clark and Kaplan[25] in serum sickness. Friedberg and Gross[27] reported four cases in which periarteritis nodosa and rheumatic heart disease were associated. In one of these cases there were "glomerular lesions resembling those of subacute diffuse glomerulonephritis of the intracapillary type." In discussing these two processes they state: "In both instances one is dealing with a disease of unknown etiology. Both have been considered by definite groups of investigators to be the expression of an allergic reaction in a person sensitized to more than one agent rather than the result of infection by one specific organism." It would be of considerable interest at this time to know if these patients with periarteritis nodosa associated with rheumatic heart disease received any of the sulfa drugs.

Lichtwitz[28] has expressed the opinion that glomerular nephritis occurs infrequently with rheumatic fever. He says "though vascular allergy is an important feature of rheumatic pathology, glomerulonephritis, which frequently is an allergic disease, occurs in rheumatic fever so rarely as to suggest that the rheumatic attack on the joints or on the heart precludes a like attack on the kidney."

Cases II and III are similar in that both had acute bacterial endocarditis on the right side of the heart produced by streptococci. The glomerular lesions were identical. In each case there was evidence of periarteritis nodosa. Both patients were treated with sulfa drugs. From these two cases one cannot determine with any degree of certainty the rôle played by either sensitivity to the streptococcus or sensitivity to the sulfa therapy; however, it is interesting to find evidence of sensitivity to sulfa in these two cases of intracapillary glomerular nephritis. There also is evidence of sensitivity and intracapillary glomerular nephritis in Case I. It is suggested that care should be used in administering any of the sulfa drugs to patients who have a history of allergy; furthermore, the three cases

reported in this paper should emphasize its possible effect in cases of glomerular nephritis. Williams and associates[29] treated a small group of patients with acute glomerular nephritis with sulfanilamide in 1943 and concluded that their results were most satisfactory. Murphy and Wood[30] likewise obtained good results by treating a small group of patients with acute glomerular nephritis with sulfonamides. There is no record in the aforementioned studies that the patients had received sulfa previous to this treatment for nephritis. It may be shown subsequently that only a small percentage of patients with glomerular nephritis develop periarteritis nodosa; however, this relationship apparently deserves further study.

SUMMARY

Three cases are reported of glomerular nephritis in which there were other pathologic lesions similar to those reported in cases of sensitivity to sulfa drugs. In two of these streptococcic endocarditis was present on the right side of the heart. Since glomerular nephritis is considered to be the result of a sensitivity reaction, the problem of use of sulfa drugs in diseases resulting from hypersensitivity is discussed. It is pointed out that a patient who becomes sensitized to one antigen may also become sensitive to a second antigen. Because of this, sulfa drugs should be used more carefully.

REFERENCES

1. Forbus, Wiley D. Reaction to Injury. Baltimore, 1943. Williams and Wilkins Company.
2. Longcope, W. T. Production of experimental nephritis by repeated protein intoxication. *J. Exper. Med.*, 18: 678, 1913.
3. Hansen, Pruss O. G., Longcope, W. T. and O'Brien, D. P. Skin reactions to filtrates of hemolytic streptococci in acute and subacute nephritis. *J. Clin. Investigation*, 7: 543, 1929.
4. Long, E. R. and Finner, L. L. Experimental glomerulonephritis produced by intrarenal tuberculin reaction. *Am. J. Path.*, 4: 571, 1928.
5. Lichtenstein, Louis and Fox, Leon J. Necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following administration of sulfathiazole: report of a case. *Am. J. Path.*, 22: 665, 1946.
6. French, A. J. Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfanamide chemotherapy. *Am. J. Path.*, 22: 679, 1946.
7. More, Robert H., Gardner, C., McMillan and Duff, G. Lyman. The pathology of sulfanamide allergy in man. *Am. J. Path.*, 22: 703, 1946.
8. Rich, A. R. The role of hypersensitivity in periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 71: 123, 1942.
9. Rich, A. R. Additional evidence of the role of hypersensitivity in the etiology of periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 71: 375, 1942.
10. Rich, A. R. The role of hypersensitivity in the pathogenesis of rheumatic fever and periarteritis nodosa. *Proc. Inst. Med. Chicago*, 15: 15, 1945.
11. Marine, D. and Baumann, E. J. Periarteritis nodosa-like lesions in rats fed thiouracil. *Arch. Path.*, 39: 325, 1945.
12. Longcope, W. T. Serum sickness and analogous reactions from certain drugs, particularly the sulfonamides. *Medicine*, 22: 251, 1943.
13. Landsteiner, K. Serologic and allergic reactions with chemical compounds. *New England J. Med.*, 215: 1199, 1936.
14. Landsteiner, K. and Jacobs, J. Studies on the sensitization of animals with chemical compounds. III. Anaphylaxis induced by arsphenamine. *J. Exper. Med.*, 64: 717, 1936.
15. Horsfall, F. L. Formaldehyde hypersensitiveness: an experimental study. *J. Immunol.*, 27: 569, 1934.
16. Rackemann, Francis M. Some future problems in allergy. *South. M. J.*, 39: 497, 1945.
17. Rackemann, F. M. and Greene, J. E. Periarteritis nodosa and asthma. *Tr. A. Am. Physicians*, 54: 112, 118, 1939.
18. Riemann, Hobart A., Alison, H. Price and Peter, A. Herbert. Trichinosis and periarteritis nodosa. *J. A. M. A.*, 122: 274, 1943.
19. Seegal, B. C., Khorazo, D. and Mehlman, Jr. Local serum sickness in man following the intracutaneous injection of small amounts of antisera. *J. Allergy*, 7: 27, 1935.
20. Nelson, J. Acquired sensitivity of sulfanamide drugs. *J. A. M. A.*, 119: 560, 1942.
21. Rogers, R. J. Subacute bacterial endocarditis confined to a pulmonic valve with malformed leaflets. *J. Lab. & Clin. Med.*, 29: 825, 1944.
22. Allen, A. C. Mechanism of localization implantation of vegetations of bacterial endocarditis in the heart. *Arch. Path.*, 27: 399, 1939.
23. Held, I. W. and Goldbloom, A. A. Acute streptococcus viridans endocarditis. *Arch. Int. Med.*, 53: 508, 1934.
24. Rich, Arnold R. and Gregory, John E. The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. *Bull. Johns Hopkins Hosp.*, 72: 65, 1943.
25. Clark, E. and Kaplan, B. I. Endocardial, arterial and other mesenchymal alterations associated with serum disease in man. *Arch. Path.*, 24: 458, 1937.
26. Leary, Timothy. Early lesions of rheumatic endocarditis. *Arch. Path.*, 13: 1, 1932.
27. Friedberg, C. K. and Gross, Louis. Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease. *Arch. Int. Med.*, 54: 170, 1943.
28. Lichtwitz, Leopold. Pathology and Therapy of Rheumatic Fever. New York, 1944. Grune and Stratton, Inc.

Review

Chemotherapy of Malignant Disease*

ALFRED GELLHORN, M.D. *and* LOGAN O. JONES, M.D.

New York, New York *Charlotte, North Carolina*

STRIKING advances in surgery and radiotherapy coupled with improved diagnosis of early malignancy have markedly reduced the mortality in malignant disease in recent years.[1] However, the majority of patients with cancer can be offered only palliation, usually in the form of nursing care, non-specific supportive measures and analgesics. The magnitude of the responsibility which the medical profession faces in this connection is indicated by the estimate that there are now more than 800,000 cases of malignancy in the United States and that 185,000 persons die of cancer in this country every year.[2] It has been further calculated that only 20 per cent of persons with malignant disease are salvaged for five years by the current methods of therapy. The need for a therapeutic approach to malignancy in addition to surgery and radiotherapy is apparent.

Purgation, irrational diets, blood-letting, escharotic pastes, heavy metals, snake venoms and hundreds of other ineffectual therapeutic regimens have been used in the past in the management of disseminated malignant disease. Critical laboratory and clinical evaluations of these measures have revealed their uselessness or even harmfulness and they have been largely discarded.

In the past forty years, however, there has been ever increasing research activity in the field of cancer chemotherapy. The rate at which advances have been made in this branch of experimental therapeutics in the past decade has been so rapid that it seems justifiable to anticipate, with guarded optimism, an entirely new therapeutic approach to the problem of disseminated malignant disease.

It is the purpose of this paper to assemble the evidence that is available concerning a number of carcinolytic agents. It is hoped that a review of this subject will clarify the indications for certain chemotherapeutic agents of demonstrated value, and also provide a general background which may be useful in evaluating the significance of advances yet to be made.

PRODUCTS OF MICRO-ORGANISMS

Background and Rationale. During the past eighty years there has been continuous investigation of the effects on malignant cells of products of micro-organisms. In 1868 Busch[3] reported on the dramatic regression of inoperable sarcomas in two patients coincident with an erysipelas infection. At this time the organism producing erysipelas had not yet been isolated so that efforts by Busch to produce erysipelas in other patients with malignant disease were unsuccessful. Following his demonstration of a streptococcus as the cause of erysipelas, Fehleisen[4] injected cultures of these living organisms for the treatment of human cancer with encouraging results.

The experimental studies on bacterial products as carcinolytic agents was instituted by Spronck in 1892.[5] Injecting sterile filtrates of "Streptococcus erysipelas" into dogs with spontaneous malignant tumors, he observed degenerative changes in a majority of the tumors. Beebe and Tracy in 1907[6] extended the experimental in-

* From the Departments of Cancer Research and Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. This survey was prepared in connection with work supported by the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

vestigations by using bacterial filtrates prepared from cultures of Bacillus coli communis, Staphylococcus pyogenes aureus, "Str. pyogenes" and B. prodigiosus, studying their effects on transplanted lymphosarcoma in dogs. Their results were provocative, in that softening of the tumors was noted frequently and occasional tumors regressed completely. In the succeeding quarter of a century there was little experimental activity in this approach to tumor chemotherapy, but interest was revived by the report of Gratia and Linz in 1931.[7] These investigators had been studying the Shwartzman phenomenon under a variety of conditions and were impressed by the tissue localization which could be achieved by appropriate technic. They injected bacterial filtrate from B. coli directly into transplanted liposarcoma in guinea pigs. Twenty-four hours later the same filtrate was injected intravenously, following which they observed extensive hemorrhage and necrosis in the tumor masses but not in other tissues. In another series of experiments they discovered that it was not necessary to inject the filtrate into the tumors inasmuch as the same violent intratumor reaction occurred following intravenous injection alone. In the next year Shwartzman and Michailovsky[8] reported that parenteral administration of a filtrate of meningococcus culture produced the same specific changes in mouse sarcoma 180 noted by Gratia and Linz. These observations were confirmed by Shear.[9,10]

Following parenteral injection of a potent antitumor bacterial filtrate, progressive hemorrhage with histologic evidence of tumor disruption during the first twenty-four hours was noted. At this time, however, most of the malignant cells appeared viable. After twenty-four hours extensive necrosis of neoplastic cells was apparent. Gross observation showed the formation of a dry hemorrhagic scab with a surrounding zone of apparently active growth. In the course of seven to ten days the necrotic material sloughed leaving a bed of granulation tissue which in many instances went on to complete healing. Microscopically, there was a sharp line of demarcation between necrotic tumor cells and actively proliferating cells. In the course of the week after injection all tumor cells within the necrotic circle became poorly stained or fragmented and disappeared.[11]

Shear and his associates[12,13] subsequently demonstrated that a filtrate of Serratia marcescens (B. prodigiosus) cultures is also a potent agent, inducing hemorrhage and necrosis in subcutaneous mouse carcinomas. Over a period of several years they fractionated and purified this material until an extremely active preparation was obtained which produced tumor hemorrhage and necrosis when injected into mice in dosages as small as 0.1 microgram.[14] The highly purified fraction has been characterized chemically and has been found to be a polysaccharide.[15] Shear and his co-workers have explored with thoroughness the potentialities and limitations of the hemorrhage-producing bacterial polysaccharide in the chemotherapy of experimental neoplasms. From their reports[16] it can be concluded that the polysaccharide produces specific changes in a variety of tumors, including both transplanted and primary sarcomas as well as primary carcinomas. The toxicity of the polysaccharide was found to be greater in tumor-bearing mice than in normal animals, and the toxicity in the tumor mice was directly related to the size of the neoplasm being treated. Thus, it was demonstrated that the lethal effect in these mice was due to hemorrhage and necrosis in the tumor with secondary absorption of toxic products from tumor breakdown in addition to primary polysaccharide toxicity. It was noted further that some portion of the neoplasm almost invariably escaped destruction and that areas of tumor unaffected by the initial dose were resistant to the action of subsequent doses. In the few instances in which the entire tumor was involved in the hemorrhagic and necrotic process the animals developed signs of severe intoxication followed by shock and death.

Besides the observation that many species of bacteria are capable of elaborating substances which induce hemorrhage and necrosis in tumors, attention has been called to the fact that spirochetes causing relapsing fever (Borrelia recurrentis)[17] and tick fever (Bor. duttoni)[18] produce regressive effects in experimental tumors. Of particular interest because of its current clinical application, is the work of Roskin and his collaborators.[19–21] These workers undertook a systematic study of the influence of various infections and toxins on transplanted cancer. They finally selected Schizotrypanum cruzi because they found that in mice the spirochete localized and proliferated chiefly in certain organs rather than in the blood stream, resulting in a more chronic course than was obtained with other experimental infections. They observed that when mice were infected with S. cruzi and at the same time inoculated with Ehrlich carcinoma the development of both the infection and the tumor was depressed as compared with control groups of mice. The natural course of simultaneous infection and malignancy in mice was a gradual increase in the infection with eventual death of the animals; in the terminal stages of the infection the tumor either markedly regressed or disappeared. From these experiments they concluded that the trypanosome infection exerted an antagonistic action on mouse cancer. However, since it was considered possible that the carcinolytic effect thus observed was a result of deprivation of nutrient substances necessary to the malignant cells due to exhaustion of the host by the overwhelming infection, studies were undertaken to avoid this complication. In a series of experiments it was reported that heat killed S. cruzi suspended in plasma or saline exhibited a marked inhibitory and lytic effect on the experimental tumor without producing histologically recognizable damage to normal structures.

The experimental observations of Roskin have been supported by Malisoff who reported that "whole culture lysates" of Trypanosoma cruzi had regressive effects on experimental tumors.[22] However, Hauschka and his associates,[23–26] using eight strains of T. cruzi including those employed by Roskin and Malisoff, could demonstrate no significant retardation of the growth of five experimental malignant neoplasms. The carefully controlled and exhaustive study of these investigators constitutes formidable evidence against the existence of a carcinoclastic endotoxin in T. cruzi.

Cohen et al. have studied the effects of a variety of microorganisms, including three strains of T. cruzi, on the growth of tumor cells *in vitro* with negative results.[27]

Mechanism of Action. The mechanism of the production of hemorrhage and necrosis in various neoplasms by a variety of bacterial filtrates is not altogether clear. In order to understand the experimental evidence which has been gathered on this point it is necessary to review briefly two reactions of hypersensitivity, the Arthus phenomenon and the Shwartzman-Hanger phenomenon.

In 1903 Arthus[28] published the results of experiments on rabbits which had received repeated parenteral injections of ordinarily non-toxic foreign protein. When after a variable period ranging from ten days to months or even years a subcutaneous injection of the same foreign protein was given, there followed hemorrhage, edema and finally, in the course of about two days, necrosis with the formation of a sterile abscess at the site of injection. Subsequently, it has been demonstrated that any organ or tissue of a sensitized animal if brought into contact with the specific antigen will exhibit a violent inflammatory response. There is ample evidence that the Arthus phenomenon is an expression of local anaphylaxis, that is, the response to the local reaction of antigen and tissue antibody.[29]

Shwartzman and Hanger working independently published almost simultaneously the results of experiments on local skin reactivity elicited in a different fashion.[30,31] They observed that when certain bacterial

filtrates (chiefly culture filtrates of gram-negative organisms) were injected into the skin of normal rabbits, and this was followed in from four to forty-eight hours by an intravenous injection of the same or different filtrates, an intense skin reaction occurred at the site of the original skin injection. The local site at first became hemorrhagic and in a majority of cases necrosis followed. The mechanism of local tissue reactivity to bacterial filtrates cannot be stated with precision. Evidence has been gathered to show that it is not due to local blockade of reticulo-endothelial cells and is not due to inflammation or to increased capillary permeability.[32] It therefore becomes necessary to assume that the reactivity is due to some functional disturbance in the cells induced by a variety of, but not all, bacterial filtrates. Further, the injury can be inflicted on the reactive cells only when the provocative material is present in the general circulation.

There are several striking differences between the Shwartzman-Hanger phenomenon of local tissue reactivity and the Arthus phenomenon of local anaphylaxis: In the former the incubation period necessary to elicit the local skin reactivity is about twelve hours and no response can be produced if the local and intravenous injections are separated by more than forty-eight hours, whereas the incubation period for local anaphylaxis is about ten days and sensitivity lasts for months or years. Also the Arthus phenomenon is highly specific in that the antigen used to sensitize the animal must also be used to elicit the response; in contradistinction, culture filtrates of unrelated organisms can serve in demonstration of the Shwartzman-Hanger phenomenon. Whereas any antigenic substance can elicit local anaphylaxis, the local skin reaction can be produced only by certain bacterial filtrates. Finally, the Shwartzman-Hanger phenomenon cannot be transferred passively.

From the foregoing discussion it is immediately apparent that the hemorrhage and necrosis occurring in malignant tumors following intravenous administration of an appropriate bacterial filtrate is not related to local anaphylaxis, inasmuch as there is no evidence to indicate that the various bacterial toxins are identical with any potentially antigenic constituent of neoplastic cells.

The relationship of the toxin-induced tumor reaction and the Shwartzman-Hanger phenomenon would appear to be close and yet there may be some fundamental differences. In this latter connection it is to be noted that hemorrhage and necrosis in tumors may be induced by intravenous or intraperitoneal injection of a bacterial filtrate without preliminary introduction of the material locally. This apparent fundamental difference in the two phenomena was investigated by Duran-Reynals[33] who explored the possibility that the tumors had been appropriately sensitized due to secondary bacterial infections in tumor-bearing animals. He found, however, that tumors without previous bacterial infection reacted strongly to the effect of active bacterial filtrates. Gratia and Linz assumed that the state of reactivity of tumors was related to the hypothetical virus inducing tumor formation. This is difficult to accept inasmuch as no virus has been identified in tumors in which one obtains the reaction. In addition the Shope papilloma, which is apparently produced by a virus, remains totally resistant to the effects of the active bacterial principles. Further conclusive evidence against this hypothesis is afforded by the fact that tumors induced by local application of carcinogens are susceptible to the bacterial filtrate reaction. The possibility has been considered that rapidly proliferating blood vessels of neoplasms are more susceptible to the injurious effects of bacterial substances than the blood vessels of normal tissue. Support of this hypothesis is provided by the fact that the active principles of bacterial filtrates which elicit the dramatic effect on tumors produce no demonstrable effect upon the blood vessels and tissues remote from the tumor.[34] However, it is difficult to explain why such

strong capillary poisons as gold chloride[34] or histamine[35] fail to affect the neoplasm while in the same animal their characteristic action on normal capillary beds is demonstrable. Also various granulomas, teratomas and all benign neoplasms which may have rapidly proliferating vascular channels are totally resistant to the active principles.[33,36]

It must be concluded that the tumor reaction and local skin reaction of Shwartzman and Hanger are related to the inherent toxicity of active principles contained within or obtained from bacterial filtrates. There are obvious differences between the two reactions but the fact that there is a definite correlation between the ability of a filtrate of a given micro-organism to elicit the phenomenon of local tissue reactivity in rabbits and the inhibiting effect of this same filtrate upon experimental tumors[14] argues for closely related mechanisms.

Clinical Application. The extensive experimental investigation of the tumor-inhibiting action of bacterial filtrates stemmed from the clinical observation of Busch[3] as has already been mentioned. The major advocate of this form of therapy was Coley, who started treating malignancy in this way in 1891 and was still reporting the results of therapy at the time of his death in 1935.[37,38] The published clinical evidence on the use of bacterial filtrates has recently been compiled[39] from the time that Coley utilized the mixed toxins from "S. erysipelas" and B. prodigiosus until the introduction of the highly purified and potent polysaccharide obtained from culture filtrates of S. marcescens by Shear. It is difficult to assess with any confidence the significance of toxin therapy in the reported results because in a large proportion of the cases therapy with toxin was combined with surgery or x-radiation.

Although we are unable to evaluate toxin therapy satisfactorily during the period from 1892 to 1935, we can inquire why it was not more popular and why since 1942 no commercial preparation of bacterial toxins has been available. Seven years after Coley instituted toxin therapy with a mixed filtrate of "S. erysipelas" and B. prodigiosus (Serratia marcescens), a toxin product from the same organisms was commercially prepared. On the basis of clinical observation Coley was convinced that the commercial preparation was far less potent than the mixed toxins which he had been using. Coley and a few other clinicians used a more stable and more potent preparation made by Tracy.[40] However, the majority of physicians who attempted chemotherapy of malignancy with "Coley's fluid" had only relatively impotent commercial preparations available. It would therefore appear that one factor to account for the discontinuance of bacterial filtrate therapy was the high variability in the potency of the therapeutic agent. Also since the experimental evidence on the inhibition of tumors by bacterial filtrates was scanty, the importance of bringing the toxin into contact with the neoplasm via the general circulation was not appreciated. Even the chief advocate of toxin therapy, Coley, administered the mixed toxins either into the tumors directly or intramuscularly. Finally, an important deterrent to the general acceptance of toxin was the marked systemic reaction which occurred in most patients treated. This consisted of a chill followed by a temperature elevation of 102° to 104°F. The fever persisted from twenty-four hours to four days. According to the description of Fowler,[41] when hemorrhage and necrosis occurred in neoplasms with extensive distribution there was evidence of hemolysis in the general circulation, presumably as a result of absorption of toxic products of tumor breakdown.

More recently Brues and Shear reported on the toxic reactions to bacterial filtrates.[42] Using the highly purified and potent tumor-inhibiting polysaccharide from S. marcescens, these investigators treated (by intramuscular injections) four patients with advanced malignancies (prostatic carcinoma, lymphosarcoma, multiple myeloma and Ewing's sarcoma). All of these patients died with tumors. Two patients showed

noteworthy relief of symptoms; two patients showed evidence of hemorrhage in tumors at necropsy although it was not possible to decide whether this finding was related to treatment. The patient with multiple myeloma showed no evidence of any effect of this agent on the course of the disease. More significant than the fact that therapy was disappointing were the toxic manifestations induced by the drug. In all instances there was an initial chill followed by fever as high as 107°F. A prolonged period of hypotension occurred, sometimes with anuria and cardiac decompensation. There was an elevation in the blood uric acid and increased uric acid excretion in two patients which was considered to be suggestive evidence of tissue breakdown. It is of interest that the chemical evidence of possible rapid breakdown of nitrogenous substances occurred in the two patients who also had symptomatic relief from therapy. Holloman[43] and Oakey[44] have extended the clinical observations on the effect of the polysaccharide from S. marcescens. Their studies differed from those of Shear and Brues in that the polysaccharide was injected intravenously. Essentially the same manifestations were observed following intravenous injection of the polysaccharide as after intramuscular injection. These included hyperpyrexia to as high as 108.4°F., hypotension to shock levels, leukocytosis and frequently pain in the region of the tumor. The hypotension was apparently due to vasodilation and was best controlled by administration of epinephrine.

Included in the seventeen patients treated by Holloman and Oakey were cases of sarcoma (of both soft tissue and bone), malignant lymphoma (Hodgkin's disease and lymphosarcoma), malignant melanoma and leukemia. In a number of instances serial biopsies were taken, and these disclosed intratumor hemorrhage in every instance. Although multiple injections of polysaccharide were employed in several of the patients, none of them was followed sufficiently to evaluate the efficacy of therapy, the primary objective of the investigation being to study the toxicity of the drug.

At the present time there is inadequate information available on the application of S. cruzi endotoxin in the therapy of human neoplastic disease. Klyueva[45] recently briefly summarized the results of treatment in nineteen patients with carcinoma of the larynx, carcinoma of the cervix, carcinoma of the breast and carcinoma of the lip. Injections of the endotoxin, which is called KR (Klyueva-Roskin), by the subcutaneous, intramuscular or intratumor route were followed by pain at the site of the malignancy. After a variable period of time there was disintegration of the neoplasm with localized suppuration. Since the author does not provide details of the follow-up, it is impossible to evaluate the results objectively. Klyueva reports a favorable response in the majority of patients.

Comment. The foregoing comments indicate the extensive investigations which have been carried out on the effects of microbial products on neoplastic disease. From the experimental observations there can be no doubt that profound alterations of malignant cells may be induced by these products. It is clear that their application in human neoplastic disease for the present is hazardous and of doubtful efficacy. The preparations which have been used are still in a relatively crude state, however, and it is possible that further fractionation and precise chemical characterization will lead to elimination of the components which produce toxic reactions and also to further concentration of the active carcinolytic principles.

ANTIRETICULAR CYTOTOXIC SERUM

Background and Rationale. The significant contribution of the reticulo-endothelial system in cellular and humoral immunity is well established. There are also other physiologic mechanisms in which this system participates. These include (1) erythrocyte phagocytosis and the metabolism of hemoglobin and bile; (2) repair and regeneration of tissues and (3) lipoid storage

metabolism. Of particular interest in connection with this discussion is the evidence for the part played by the reticulo-endothelial system in limiting neoplastic growth.

There are at least two types of study which circumstantially implicate the reticulo-endothelial system as an important deterrent to neoplastic growth and development.[46] Morphologic examination of this widespread system in experimental tumor-bearing animals has revealed a marked hypertrophy under certain circumstances, particularly of the elements in the liver and spleen. This is manifested by proliferation of histiocytes and Kupffer cells in the liver and by reticular hyperplasia of the spleen. It would also appear significant that a correlation exists between the reaction of the follicular elements of the spleen in animals treated with chemical carcinogens and the incidence of tumor production in these animals. In refractory animals there is marked hyperplasia of follicles and of reticulo-endothelial elements whereas in those animals in which a malignancy is produced follicular aplasia of the spleen is noted.[47] In addition to these histologic findings the gross anatomy of the spleen has been found to be abnormal inasmuch as hypertrophy resulting in an increased weight of the organ has regularly been observed in animals bearing various types of neoplasms.[48–50] It has been further demonstrated that splenic hypertrophy can also be induced in animals by means of injections of blood derived from animals or humans with malignancy.[51] Recently this has been employed as a diagnostic test.[52] Splenic hypertrophy in experimental animals with tumors is interpreted as an expression of a physiologic defense mechanism. It is noteworthy in this regard that malignant tumors rarely metastasize to the spleen, a fact which is striking in view of the rich supply of blood and lymph vessels to this organ and its anatomic proximity to gastrointestinal organs which are so frequently affected by malignancy. In a survey of 580 autopsies of cancer patients only 3.2 per cent showed splenic metastases.[53]

When the function of the reticulo-endothelial system is depressed, either by splenectomy or by functional impairment of the elements caused by loading them excessively with certain colloids, there appears to be stimulation of tumor development and growth. Thus, Andervont[54] demonstrated that when mouse tumors were grafted to mice of another strain they grew far better and faster if the recipients had previously been injected with trypan blue. Similar observations have been made with chemically induced tumors; the development and growth of tumors due to coal tar or dibenzanthracene were found to be accelerated and increased in splenectomized mice as compared with the response in control animals.[55]

However, it is impossible to accept without question the hypothesis that the cells of the reticulo-endothelial system elaborate some principle which possesses growth-inhibitory and/or lytic properties for neoplastic cells. It is, for example, difficult to reconcile with the alleged carcinoclastic activity of the reticulo-endothelial system the characteristic infiltration of lymph nodes, liver and spleen by the malignant lymphomas. Also it has been demonstrated that tumors and spleen can be cultivated in the same tissue culture medium without significant depression of the growth rate or characteristics of either tissue.[56,57]

Historically, the development of antireticular cytotoxic serum stems from the teaching of Metchnikoff which emphasized the pharmacologic principle that small doses of a toxic drug may stimulate cell functions rather than depress them. Metchnikoff reasoned that it should be possible to stimulate the function of a tissue by administration of small doses of antiserum specific for the tissue. Parenthetically, it is to be noted that in the light of present day knowledge of mechanisms of drug action the pharmacologic principle enunciated by Metchnikoff is increasingly difficult to defend. Bogolomets, a student of Metchnikoff, postulated that because of the pervasiveness of the reticulo-endothelial system

and the multiplicity of its functions, the functional state of this system was a major determinant of health and of resistance to infection and degenerative disease. He further believed that the functional capacity of the physiologic system in man could be improved by administration of small or stimulating doses of a cytotoxic serum produced in animals by injection of antigens prepared from organs rich in reticuloendothelial tissue. He prepared such a serum for human use by inoculating horses with the cells of spleen and bone marrow from human cadavers. The experimental observations and clinical applications of antireticular cytotoxic serum were carried out exclusively in the U.S.S.R. until very recently. These have been summarized in detail by Bogolomets[58] and Straus.[59] Suffice it to say that at a conference held in Russia in 1942, at which time 2,500 clinical observations were surveyed, it was concluded that the therapeutic effect of ACS was clearly established in war traumatisms and in the following diseases: (1) frostbite and wounds, especially slowly knitting bone fractures and indolent, infected wounds; (2) infectious diseases, especially typhus; (3) diseases of the nervous system, especially traumatic and infectious diseases; (4) diseases connected with disordered trophic functions of tissue, especially peptic ulcers.

Fedyushin and Bogolomets demonstrated that small doses of ACS significantly decreased the number of "takes" of transplanted cancer, caused the disappearance of large cancers already present and reduced the number of metastases in mice.[60]

The claims for antireticular cytotoxic serum have been investigated experimentally in this country by Straus and his colleagues.[61,62] On the basis of enthusiastic statements of a number of Russian investigators regarding the favorable effects of small doses of ACS on the rate and extent of healing of fractures, these authors carried out a series of observations on experimental fractures in the rabbit. ACS was prepared in rabbits and goats using human spleen and bone marrow for the antigen. The titer of ACS was determined by a complement fixation technic described by Marchuk.[63] In 156 rabbits with experimental fractures the authors investigated the effects of stimulating doses of ACS (0.00125 ml., titer 1:320) and depressing doses of the same serum (0.1 ml.) on (1) x-ray changes of the healing fracture sites, (2) gross and microscopic alterations of the bones and (3) breaking strength of the healed fractures. Although there were no apparent differences in the first two criteria just mentioned, statistical evaluation of the breaking strength of the healed fractures indicated highly significant differences between each of the groups and its control.

From these results the authors conclude that "stimulation of the healing of experimentally produced fractures in rabbits was induced with small (stimulating) doses of antireticular cytotoxic serum and depression of healing followed large (depressing) doses as claimed by the Soviet investigators."

Mechanism of Action. The mechanism of action is completely unknown. The experimental observations discussed in the foregoing section (which have not been confirmed) would indicate that there is a lack of specificity of the action of ACS inasmuch as human antigen was employed to produce the antibodies and these presumably stimulated or depressed the rabbit reticuloendothelial system.

Clinical Application. Use of antireticular cytotoxic serum in the therapy of malignant disease has been reported only in summary form by the Russian investigators.[58] In this country Davis[64] has made a preliminary but unpromising report on his experience with the material in a variety of neoplasms and Friedman and Stritzler reported a negative result in mycosis fungoides.[65] Skapier[66] has treated twenty-two cases of Hodgkin's disease. There was no evidence that a fundamental effect on the neoplasm was produced although transient weight gain and decrease in the erythrocyte sedimentation rate was noted. Because of the paucity of objective data, it is impossible at this time to assess the contribution if any

to the chemotherapy of cancer made by this approach. Rogoff and his associates[67] attempted without success to confirm Russian claims of striking benefit of ACS in arthritis.

Comment. Antireticular cytotoxic serum has been presented in detail primarily as an example of many investigations which stem from the hypothesis that the reticuloendothelial system is a significant barrier to the development and/or spread of malignant disease in man. This hypothesis, which lacks convincing proof, has been repeatedly advanced to provide the rationale for the therapy of malignant disease with organ extracts. The most recent report of this nature is that of Watson, Diller and Ludwick[68] who advance inconclusive evidence that an extract of calf spleen alters the course of human malignancy. Another example of a chemotherapeutic agent stemming from the same hypothesis is teropterin which is to be discussed in the next section.

FOLIC ACID CONJUGATES

Background and Rationale. Lewisohn and his associates have devoted their research efforts over a period of years to the therapy of transplanted and spontaneous tumors in mice. In 1938 they reported that an extract of beef spleen caused regression in a significant number of instances of sarcoma 180.[69] An extract of mouse spleen was found to have a cytotoxic effect on spontaneous breast carcinoma in mice. Due to the impracticality of large scale extraction of mouse spleens, extracts obtained from a number of other sources were screened for their antitumor activity. The attention of this group of investigators was focused on the components of vitamin B complex by their observation that extracts of barley and brewers' yeast seemed to cause regression of spontaneous mammary adenocarcinoma in mice.[70] In 1945 the Leuchtenbergers, Lazlo and Lewisohn[71,72] reported that L. casei fermentation factor caused complete regression of 30 per cent of spontaneous breast cancers in three different strains of mice treated with daily intravenous injections of 5 micrograms of the material. At the time of their report this was considered to be pteroylglutamic acid, i.e., folic acid. Subsequent chemical characterization of the L. casei fermentation factor showed this to be a folic acid conjugate, pteroyl triglutamic acid. Folic acid was ineffective.[73]

The results of the experimental chemotherapy of Lewisohn and his co-workers could not be confirmed by Sugiura,[74] Burk[75] and Morris.[76]

Mechanism of Action. No mechanism of action has been suggested.

Clinical Application. Farber and his associates published a preliminary report on the use of pteroyl glutamic acid conjugates in malignant disease in man.[77] Their series of patients treated with teropterin and diopterin (pteroyldiglutamic acid) includes acute leukemia; astrocytoma; Ewing's tumor; carcinoma of the rectum, colon, stomach, cervix, prostate, pancreas, esophagus, bladder, breast, gallbladder, kidney and ovary; Hodgkin's disease, lymphosarcoma; osteogenic sarcoma; ependymoma; leiomyosarcoma of the stomach; spongioblastoma multiforme; seminoma; hypernephroma; chondrosarcoma; epidermoid carcinoma of the pharynx and of the tongue and embryoma of the kidney. The authors stated that, in general, the patients experienced "improvement in energy, appetite and sense of well being." Since no details of the cases were presented, it is impossible to evaluate the effect of therapy in their patients. It is noteworthy that in eleven patients from whom serial biopsies were obtained before, during and after teropterin therapy there was "no change in the tissues which could be regarded as a deleterious effect of the substance employed." The authors conclude that the drug is non-toxic and since there were instances of improvement which seemed to be greater than could be accounted for by the concomitant conventional therapy (such as radiotherapy), they suggest further clinical trial.

Additional evidence on the efficacy of teropterin in human neoplastic disease was presented by Klainer,[78] Lehv and his co-

workers[79] and Meyer[80] at a recent symposium devoted to the effect of derivatives of folic acid on certain types of neoplastic disease. Although more details of the subjects treated were given in these latter reports, only a limited number of patients were studied for short periods of time. For the most part the patients were receiving other forms of therapy at the same time that teropterin was being employed which makes it difficult to evaluate the contribution of the drug in question. There was no objective evidence recorded which indicated that the course of the neoplastic diseases studied had been significantly altered.

Comment. This brief summary of the current status of pteroyl triglutamic acid in the chemotherapy of malignant disease was included only because teropterin has recently received considerable publicity in the lay press as a significant contribution to this serious problem.

It has been demonstrated that man is well equipped with enzymes, so-called conjugases, which efficiently split folic acid conjugates with the release of folic acid.[81] Administration of pteroyl triglutamic acid parenterally therefore presumably results in the removal of two glutamic acid molecules *in vivo*, leaving folic acid. This vitamin has been shown to play a significant role in the maturation of cells of the hemopoietic system. Since there is no evidence that malignant disease is an expression of a folic acid deficiency, there is no apparent rationale for teropterin therapy.

The only experimental evidence that teropterin has a cytotoxic action on malignant cells is the unconfirmed work of Lewisohn and his associates. Woll[82] and Little et al.[83] have shown that the growth of the Rous chicken sarcoma is actually stimulated by folic acid and inhibited by folic acid antagonists.

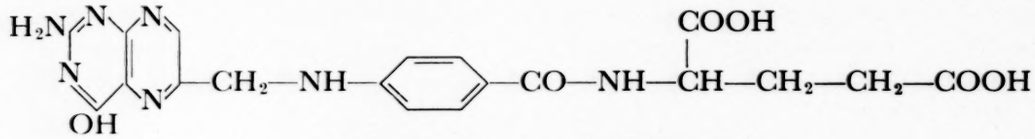
At the present time there is no evidence from the reported clinical trials with teropterin that this drug affects human neoplastic growth or significantly alters the course of malignant disease in man. The Council on Pharmacy and Chemistry of the American Medical Association reached the same conclusion on the basis of reports which it received on the results of teropterin and diopterin therapy in 275 patients.[84]

However, the Council noted that relief of pain and subjective improvement was reported in 50 per cent of the patients. It was considered possible that this analgesic action, particularly of teropterin, might offer a significant advantage over the narcotics because of the absence of side reactions, addiction and hypnotic effects. Inasmuch as the psychotherapeutic factor associated with the use of a new form of therapy was not controlled in these studies, it is not permissible to accept the alleged analgesic action of the folic acid conjugates as a fact. In the absence of either conclusive experimental or clinical demonstration that these compounds have any fundamental influence on malignant disease the authors believe that the implications in the lay press and in the advertising to the medical profession are unfortunate, misleading and unwarranted.

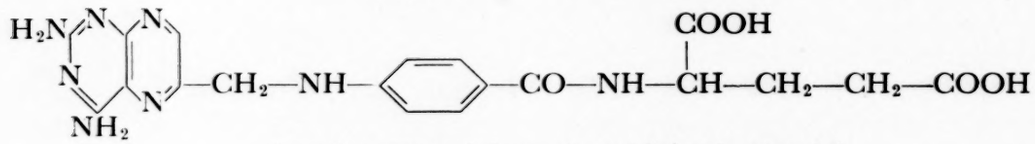
FOLIC ACID ANALOGS

Background and Rationale. The development of metabolic antagonists in the form of chemical analogs of essential metabolites has provided significant research tools for the classification of a variety of physiologic cellular mechanisms.[85] As each new member of the vitamin B complex has been chemically characterized one or more chemical analogs has been synthesized. Numerous analogs of pteroylglutamic acid have been prepared and a number of them have been found to be potent folic acid antagonists as indicated by their ability to prevent the growth of Str. faecalis R when added to culture media rich in folic acid.[86,87] The two types of analogs which are pertinent to this paper are those in which the substituents of the pteridine ring of folic acid are either changed or other groups added, and those in which besides these alterations the glutamic acid is substituted by another amino acid. The chemical relationship of the analogs to folic acid can

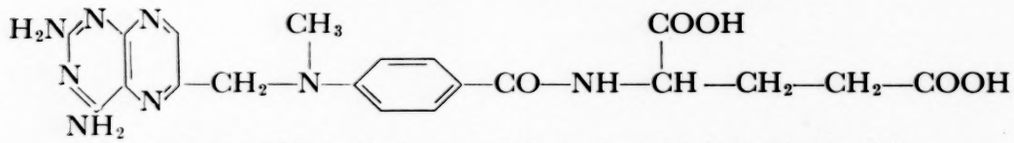
best be illustrated by the structural formulas of the drugs which are currently receiving extensive clinical trial in cancer chemotherapy.



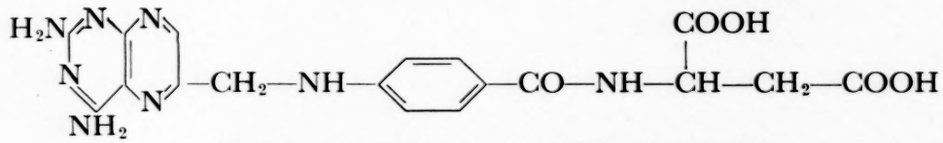
Pteroylglutamic acid (folic acid)



4-amino-pteroylglutamic acid (aminopterin)



4-amino-N^{10} methyl-pteroylglutamic acid (α-methopterin)



4-amino-pteroylaspartic acid (amino-an-fol)

In the clinical trials with the folic acid conjugates Farber and his associates noted that the course of the disease in patients with acute leukemia appeared to be accelerated. The apparent stimulation of abnormal leukocyte production in the bone marrow led him to the hypothesis that folic acid was an essential metabolite for leukopoesis. On the basis of these observations he instituted clinical trials with folic acid antagonists in acute leukemia.

Mechanism of Action. As has been mentioned in the preceding sections it has been demonstrated that the folic acid analogs act as antagonists in certain biologic systems. This can be shown clearly in the case of certain bacteria (S. faecalis R) which require folic acid for their growth. It has also been shown that the growth rate of the Rous chicken sarcoma can be significantly depressed by administration of folic acid analogs to the host and can be accelerated by feeding diets high in pteroylglutamic acid.[82,83] However, these latter observations cannot be accepted as evidence that neoplastic cells are dependent upon folic acid for it is known that this tumor is caused by a filterable virus. The mechanism of action of the folic acid analogs in human neoplastic disease is not known, but as will be seen in the succeeding section circumstantial evidence indicates that it is unrelated to folic acid antagonism.

Clinical Application. Farber, Diamond et al.[88] have made a preliminary report on the immediate results of treatment with aminopterin in sixteen cases of acute leukemia in children. In ten of these patients clinical and hematologic remissions occurred during therapy with the folic acid analog for intervals ranging from two weeks to six months. The remaining six were either unimproved or made worse. Careful analysis of these cases by the Boston group has led them to the conclusion that the remissions have not been correlated with either blood transfusions or infection which are important

factors associated with spontaneous remissions. The remissions have been characterized by decrease in the blasts and other immature leukocytes in both the peripheral blood and the bone marrow. Decrease in the size of subcutaneous lymph nodes and of hepatosplenomegaly also occurred and is indicative of a cytotoxic effect on leukemic infiltrations. With the onset of remission, there has also been an increase in the erythrocytes and platelets. In subsequent reports Farber stated[89] that in a much larger series "about 52 per cent" of the cases of acute leukemia in children have shown hematological and /or clinical improvement which can be classed as a remission. These patients have received α-methopterin, amino an-fol as well as aminopterin.

In the case of aminopterin the drug is administered subcutaneously or intramuscularly at daily intervals in doses of 0.5 mg. to 1.0 mg. Therapy is continued until remission occurs or until toxic manifestations appear. Evidences of toxicity include severe stomatitis, ulceration of the intestinal epithelium, pancytopenia due to bone marrow depression and alopecia. Of these manifestations stomatitis frequently occurs first and it is the signal for immediate discontinuation of the drug; after one to two weeks therapy may be resumed cautiously. Folic acid and liver extracts have been given simultaneously with aminopterin in an attempt to prevent toxicity but this has been unsuccessful.

The results of folic acid analog therapy in acute leukemia in adults have been less impressive although Dameshek[90] has stated in an editorial that in about one-third of a small series of patients there has been a significant improvement in the clinical and hematologic condition. In all cases thus far reported, including children and adults, the period of follow-up has been too brief to determine whether the course of the disease can be significantly altered by therapy with these chemicals.

It is of interest and significance that cases of Hodgkin's disease, lymphosarcoma and neuroblastoma have had temporary remissions following aminopterin therapy.[89] No detailed reports on the patients are yet available so that it is impossible to compare these results with those obtained by conventional radiotherapy or by nitrogen mustard.

Comment. It is too early to assess the significance of the folic acid analogs in cancer chemotherapy. Because of the limited understanding of the fundamental biology of acute leukemia, it is difficult to evaluate the practical importance of temporary hematologic remissions. If with further clinical experience it is demonstrated that the life expectancy of patients with acute leukemia is increased, a very significant advance in cancer chemotherapy can be claimed. At the present time the severe toxic manifestations which follow use of the folic acid analogs constitute a serious limitation to their general use.

Irrespective of their ultimate importance in clinical therapy, these drugs have great heuristic value. In connection with this the available observations indicate that their mechanism of action in human neoplastic disease is not specifically related to folic acid antagonism. This conclusion rests on the circumstantial evidence that neither the beneficial effect in certain cases of acute leukemia nor the toxic manifestations can be counteracted by simultaneous administration of folic acid.

STILBAMIDINE

Background and Rationale. In visceral leishmaniasis or kala-azar the serum globulin is usually markedly elevated.[91] Following adequate therapy with tervalent or quinquivalent organic antimonial drugs, the signs and symptoms of the disease disappear and the serum globulin level returns to normal. Following the discovery by Yorke[92] that the diamidines, stilbamidine, pentamidine and propamidine were effective chemotherapeutic agents against a number of experimental protozoal infections, these drugs were found to be active against Leishmania donovani infections in man. As with the antimonials, stilbamidine therapy

in human leishmaniasis was followed by a decrease of the elevated plasma globulins.[91,93]

In multiple myeloma the plasma globulin is frequently increased. On the basis that stilbamidine therapy of kala-azar causes a decrease in plasma globulin Snapper selected this drug for a therapeutic trial in multiple myeloma.[94,95]

Mechanism of Action. The morphology of myeloma cells secured by sternal marrow aspiration has been intensively studied by Snapper following stilbamidine therapy.[96,97] After four to six weeks of therapy basophilic granules or inclusion bodies appear in the cytoplasm of the myeloma cells of many patients. In none of the other cellular components of the marrow have such inclusions been found. Utilizing chemical and physical methods, Snapper and his associates characterized the chemical composition of the myeloma cell inclusion bodies. From a combination of specialized staining technics before and after exposure of the myeloma cells to ribonuclease it was concluded that the inclusion bodies contained ribose nucleic acid. This conclusion was confirmed by ultraviolet microscopy, in that the granules were found to have an ultraviolet absorption (2600Å) which was identical with that of ribose nucleic acid. This observation takes on added significance when correlated with the results of *in vitro* experiments by Kopac.[98] This author demonstrated that stilbamidine in high dilutions dissociates protamine ribonucleate with the release of protamines from these compounds. Stilbamidine reacts with nucleoproteins *in vitro*, an insoluble stilbamidine-ribose nucleate complex being formed. Kopac concluded that the cytotoxic effect of stilbamidine in experimental tumors[99,100] could be due to the fact that this diamidine dissociates nucleoproteins which are essential to neoplastic cells or that the nucleoproteins of neoplastic cells are more readily dissociated by stilbamidine than are those present in normal cells.

Thus, it is possible that the granules appearing in multiple myeloma cells following stilbamidine therapy are, in fact, stilbamidine-ribose nucleate complexes. In this connection it has been demonstrated that stilbamidine does localize in myeloma tissue.[97]

Clinical Application. Although stilbamidine has been given a therapeutic trial in a variety of neoplastic diseases, including lymphatic and myeloid leukemia, lymphosarcoma, Hodgkin's disease and various carcinomas, it has been found effective only in multiple myeloma.[95] Snapper[101] has reported on the results of therapy in thirty-five patients in whom the diagnosis was documented by sternal marrow biopsies. The one symptom common to all of the patients was excruciating pain which caused the majority of them to be bedridden. In 80 per cent of the cases the bone pain was either completely or partially relieved by therapy. Although the period of follow-up is too brief to assess the effect of stilbamidine treatment on life expectancy, it is apparent from Snapper's observations that the disease is halted only temporarily at best.

It was noted that in spite of evident clinical improvement in most of the cases the myeloma cells or myeloma cells with basophilic granules in the cytoplasm persisted. In addition Bence-Jones proteinuria continued and the hyperglobulinemia was not affected. Serial x-ray examinations of the skeleton did not disclose recalcification of the bone lesions, but neither was there roentgenographic evidence of progression of the disease.

During a course of stilbamidine therapy for multiple myeloma it is important that the patient be maintained on a low animal protein diet. When a normal diet is permitted, therapy is uniformly unsatisfactory.[94,95,101] The explanation for this dietary regimen is not clear, nor is there a report of the effect on myeloma bone pain of a restricted animal protein diet alone.

Stilbamidine freshly dissolved in isotonic saline is administered intravenously preferably, or intramuscularly if the subcutaneous veins are inadequate. It is irritating by intramuscular injection and it is recommended that 2 per cent procaine be added

when administration is by this route. The daily dosage suggested is 150 mg. in a single administration; the total therapeutic dose is between 3,000 mg. and 6,000 mg.

Toxic reactions to stilbamidine may be immediate or delayed. The immediate toxicity is manifested by local pain along the course of the vein, a feeling of warmth in the face and a drop in blood pressure which may be great enough to lead to syncope. This latter reaction is due to marked peripheral vasodilatation as a result of the direct relaxing effect of the drug on the smooth muscle of the arterioles. This reaction can be prevented by administration of epinephrine just before the stilbamidine injection, or the stilbamidine can be slowly injected into the rubber tubing of an intravenous saline infusion.

When stilbamidine was first used in the therapy of leishmaniasis, delayed toxic effects on the liver, kidney and nervous system were noted. It was soon determined that these were not due to stilbamidine but to a degradation product which appeared when stilbamidine in solution was exposed to light.[102] Arai and Snapper[103] have recently reported the results of careful studies of liver and kidney function following stilbamidine therapy in twenty-six patients and no significant changes were noted. The prevention of parenchymal necrosis is probably due to the fact that at the present time freshly prepared solutions of stilbamidine are used exclusively. These authors also found no significant changes in the formed elements of the peripheral blood.

A toxic reaction which has not been prevented by use of fresh solutions of stilbamidine is subjective disturbances and dissociated anesthesia of areas supplied by the sensory branches of the trigeminal nerve, which may develop two and one-half to five months after the completion of stilbamidine therapy.[104–106] The reaction is characterized by subjective symptoms of numbness, formication, heaviness and itching of the affected areas. The sensation of light touch is lost but pain, temperature and pressure modalities are intact. From experimental studies it appears probable that the symptoms and signs are due to toxic degeneration of the principal sensory nucleus of the fifth nerve. In stilbamidine intoxication in dogs neuronal and myelin disintegration have been observed in this area.[107] In Arai and Snapper's series of stilbamidine treated patients eighteen were followed for a sufficient time to evaluate the incidence of this reaction. It occurred in ten of the eighteen patients. The symptoms persisted over a protracted period and then spontaneously gradually diminished in intensity. No satisfactory therapy of this toxic manifestation was found.

Comment. The rationale for the use of stilbamidine and more recently antimonials[108] in the chemotherapy of multiple myeloma has been presented. The hypothesis rests on the assumption that the hyperglobulinemias of kala-azar and multiple myeloma are similar. We believe that use of these drugs is empiric, however, in view of the following established facts:

First, the therapeutic response of patients with kala-azar treated with stilbamidine or antimony salts is dependent on the toxic action these compounds exert on the parasite causing the disease rather than by altering serum protein synthesis. In multiple myeloma no causative organism has been implicated.

Second, careful studies on the serum of patients with kala-azar[109] and with multiple myeloma[110] have revealed certain fundamental differences in the serum proteins in these two conditions. An elevation of the euglobulin and pseudoglobulin I fractions (Howe) with normal pseudoglobulin II is commonly seen in kala-azar. In multiple myeloma, hyperproteinemia with a similar distribution of Howe and electrophoretic fractions may occur; but the studies of Gutman and his co-workers[110,111] in a series of forty-three myeloma patients indicate that in many cases Bence-Jones proteins and other abnormal protein components appear in the serum in significant concentration. Such components can, by special

technics, be readily differentiated from the γ-globulins composing the serum globulin increment in kala-azar and have an altogether different significance. Bence-Jones proteins presumably are formed by the myeloma cells and the apparent persistence of Bence-Jones proteinemia following stilbamidine therapy would seem to be significant.

Although these data lead to the conviction that the rationale proposed by Snapper for use of stilbamidine in multiple myeloma is without basis, the drug may, of course, be used empirically. Since there is ample evidence that the fundamental lesions are not significantly altered and that the abnormal serum protein patterns persist unchanged following therapy, it must be concluded that the drug merely provides symptomatic relief. In view of this and the high incidence of drug toxicity on the trigeminal nerve and the protracted duration of therapy we believe that stilbamidine therapy of multiple myeloma should be used only as a last therapeutic resort.

URETHANE

Background and Rationale. Use of urethane as a chemotherapeutic agent in malignant diseases stems from the experimental observations of Haddow and Sexton on the effect of the drug on animal tumors.[112] These investigators systematically examined the effects on the growth of experimental tumors of those drugs which had in the past been reported to have effects upon mitosis. They examined phenylurethane and its derivatives with particular care because botanists and plant physiologists had repeatedly noted the striking arrest of mitosis in the cells of the roots of cereals and other plant species. In fact, so marked was this action that Templeman and Sexton suggested use of isopropyl phenylcarbamate as a "weedicide." Although ethylcarbamate (urethane) had been found inactive against plant growth, it was not neglected by Haddow and Sexton in their screening program for carcinolytic agents. The experimental neoplasms utilized in these studies were a spontaneous mammary adenocarcinoma in mice and the Walker rat carcinoma. Several of the carbamic acid esters were found to retard growth of these tumors, urethane being the most active. In mammary carcinoma progress of the tumor was inhibited only during administration of the drug, whereas in the experiments on the Walker carcinoma a profound modification in histologic structure was produced, characterized by an apparent maturation of the undifferentiated cells. It is to be noted that death of the malignant cells was not a prominent effect of the drug on the tumor. The authors state, "Although the growth effects above described were in no way dramatic, their reproducibility, and the interest of the circumstance that they might be brought about by a known substance as simple and as readily available as urethane, suggested the advisability of testing its action in advanced and inoperable or otherwise intractable cancer in the human subject."

Mechanism of Action. The mechanism of action is unknown. It would not be justified, however, to omit mention of several possible mechanisms which have been suggested. Because urethane was widely employed in Europe as an anesthetic agent in laboratory experiments, a considerable body of information is available on the mechanisms of narcosis produced by this drug. It has been demonstrated that urethane is able to suppress nuclear and cell division of the sea urchin egg without causing an accompanying reduction of oxygen consumption.[113] This observation indicates that the drug interferes with intracellular enzyme systems which are not directly related to respiration. Experiments on brain tissue[114] and on bacteria[115] in general confirm this finding, but the specific catalytic substances whose functions are depressed are not known.

In addition to the possibility that urethane affects cell growth by the same mechanism involved in its production of narcosis Haddow and Sexton suggest that the drug might act by competing with a natural amine involved in the biosynthesis

of nucleotides. This concept is based on the isotope studies of Plentl and Schoenheimer[116] which indicated that the synthesis of nucleoproteins was not accomplished by utilization of relatively complex building blocks such as purines or pyrimidines but rather from smaller molecules such as certain amino acids. As yet there is no direct evidence for this attractive hypothesis of competition.

Clinical Application. The clinical investigation of urethane in man was initiated in 1943 by Paterson and her associates.[117] The first patients treated had far advanced malignant disease. The clinical results were disappointing; but it was noted that in some instances there was a striking fall in the leukocyte count. This suggested the trial of urethane in patients with leukemia.

Eighteen patients with chronic myelogenous leukemia were treated and at the time of the report the mean observation period was six months. There was one patient with acute myelogenous leukemia in whom the drug had no apparent effect and in whom the course of the disease was unaltered.

Conventional radiotherapy was used in six of the eighteen patients when either a trial on urethane had proved unsuccessful in reducing the count or side reactions to the drug were of such magnitude that it had to be discontinued. The dosage of urethane was, in part, determined by the tolerance of the patient. Most patients received 3 Gm. of the drug per day, but as much as 5 Gm. per day have been given. The amount of urethane necessary to produce a fall in the leukocyte count to about 20,000 per cu. mm., which was the point at which therapy was discontinued, varied within wide limits (19 Gm. to 134 Gm.). This dose could not be correlated either with body weight or with absolute decrease in the number of white cells. Considerable variation existed in the time taken for the leukocyte count to fall to the arbitrary end point of 20,000 per cu. mm. (eleven to thirty-six days, average thirty days). It was noted that immature cells were most sensitive to the drug, in that the differential white cell examinations revealed a disappearance of the myeloblasts and premyelocytes. The effect on erythropoiesis can be seen in Table 1. The spleen, markedly enlarged in all cases, was reduced after treatment, in some instances until it was no longer palpable.

In nine cases of chronic lymphatic leukemia urethane therapy alone was employed. It was found that the hematologic response to the drug was less satisfactory than in chronic myelogenous leukemia. In general the qualitative changes were similar in the two types of the disease, but the quantitative improvement in signs and symptoms was more variable in the lymphatic blood dyscrasia.

The changes in the total peripheral white count and hemoglobin, together with the clinical evaluation of the results, are summarized in Table 1.

The authors compared the urethane treatment of chronic leukemia with results which they had obtained in the past with x-ray therapy to the spleen. They concluded that the changes induced by chemotherapy and radiotherapy were strikingly similar. No significant differences were noted as regards: (1) quantitative or qualitative alterations produced, (2) duration of therapy required to produce the changes, (3) effect on splenomegaly or (4) improvement of the hemoglobin concentration. A comparison of the length of life of the patients treated by the two methods is not possible at the present time.

The observations of the British workers have been confirmed in both experimental[118–122] and human leukemia.[123–128] There are sufficient data in the reported results of urethane therapy in 108 patients with leukemia to provide an approximate evaluation of the immediate response. In forty patients with acute leukemia urethane therapy did not alter the course of the disease and no significant clinical and/or hematologic remissions were induced; in forty-six cases of chronic myelogenous leukemia the immediate response was satis-

factory in thirty (65 per cent); a satisfactory response has been reported in eleven of twenty-nine patients with chronic lymphatic leukemia (38 per cent).

In Paterson's experience[117] no significant remissions were induced in thirteen cases of advanced carcinoma of the breast or in eleven cases of miscellaneous malignant diseases, including Hodgkin's disease, lymphosarcoma, multiple myeloma, carcinoma of the rectum, malignant mixed salivary tumor or malignant seminoma. In general the observations of others corroborate these findings although it has been suggested that urethane be tried in highly anaplastic, disseminated epitheliomas.[129]

Recently Huggins[130] reported that the drug had beneficial effects on prostatic cancer with metastases. In one patient who had an advancing prostatic cancer following remission induced by castration, estrogen administration and radiotherapy, 4 Gm. of urethane daily for five days followed by a daily maintenance dose of 1 Gm. for six weeks, eliminated bone pain and caused a marked decrease in the size of the primary tumor. As with androgen control therapy the serum acid phosphatase levels fell after institution of treatment. Huggins demonstrated that the mechanism of action of ethylcarbamate was not through an antiandrogenic effect; the volume of secretion from the prostate of castrate dogs given testosterone and urethane simultaneously was not decreased below those values obtained with testosterone administration alone.

Comment. From the available evidence it may be concluded that urethane is a satisfactory therapeutic agent in producing temporary remission in chronic lymphatic and myelogenous leukemia. Whether the duration of life of leukemia patients so treated will be significantly prolonged is not yet established. On the basis of Huggins' results it would appear that ethylcarbamate may be an additional useful weapon against prostatic carcinoma. It is to be noted that use of the drug is potentially hazardous since it can produce marked depression of bone marrow function.[131]

TABLE I
URETHANE TREATMENT OF CHRONIC LEUKEMIA

	Before Treatment		Two Months after Initiation of Treatment		Six Months after Initiation of Therapy				
	Average Hemoglobin (per cent)	Average White Blood Cells (mm.^{3})	Average Hemoglobin (per cent)	Average White Blood Cells (mm.^{3})	Average Hemoglobin (per cent)	Average White Blood Cells (mm.^{3})	Improved	Unsatisfactory	Died
Chronic myeloid leukemia...	52	318,000	68	19,000	74	54,000	7	3	2
Chronic lymphatic leukemia..	56	216,000	78	25,000	64	47,000	2	3	4

Data calculated from Paterson, E., et al.[117]

ANDROGEN CONTROL THERAPY OF MALIGNANCY

Background and Rationale. Alteration of the internal environment by biologic means has dramatically influenced the treatment of inoperable carcinoma of the prostate. At the present time administration of estrogen or bilateral orchiectomy, or both, is an accepted and generally employed program of therapy for this malignancy. The rationale for this type of treatment rests upon sound physiologic observation.

As early as the nineteenth century it was noted that an interrelationship existed between testicular function and the prostate. In 1837 Civiale[132] described marked regression of the prostate in patients in whom bilateral orchiectomy had been performed incidental to herniorraphy. The common practice of orchiectomy for benign hypertrophy of the prostate in the latter part of the nineteenth century rested, in large part, upon the experimental observations of White[132] who carefully noted the effect of castration on the prostate gland of dogs. From his observations on the atrophy of glandular and muscular elements of the prostate he suggested this operative procedure for benign prostatic hypertrophy in man. By the turn of the century the operation was dropped because of unsatisfactory end results and because surgical technics for prostatectomy had been greatly improved. These early laboratory and clinical experiments demonstrated the dependency of the prostate upon normal testicular function.

Understanding of the effect of the secretion from the male and female gonads on the physiology of the prostate was extended by Huggins and his co-workers who devised a relatively simple operative procedure in dogs whereby the course of urine was deviated and the prostate was isolated from the bladder.[133] In such animals it was possible to demonstrate that castration caused complete cessation of prostatic secretion in seven to sixteen days. A similar effect was achieved by administration of estrogens to normal dogs. It was further shown that the ability of estrogen to decrease prostatic secretion and to cause shrinkage of the gland was related to its anti-androgenic action. In a castrate dog to whom androgen in the form of testosterone propionate was administered a normal or greater than normal amount of secretion was elicited and the gland grew. When estrogen was administered simultaneously with the androgen in appropriate dosage, it was possible to abolish the secretion of the gland and to reduce its size markedly. Histologic examination of the prostate gland in men subjected to orchiectomy for benign hypertrophy demonstrated principally an involution of the prostatic epithelium, with only minimal changes in the smooth muscle or connective tissue.[134]

Physiologic study of the prostate gland and of prostatic malignancy was greatly facilitated by the discovery of Kutscher and Wolbergs that normal prostatic tissue is rich in an acid phosphatase.[135] The Gutmans studied the acid phosphatase concentration in the prostate gland at different ages in the male and found that none was present in infancy but at the age of puberty the enzyme appeared in the gland. A significant contribution was added by the Gutmans when they reported that the serum acid phosphatase concentration was markedly elevated in patients with metastatic prostatic carcinoma.[136,137] Shortly thereafter, Gomori[138] demonstrated the enzyme by histochemical technics in the prostatic epithelium of normal males and also its presence in high concentration in the epithelial cells of prostatic carcinoma.[138]

In 1941 Huggins and his associates[139,140] assembled the available evidence on the physiology of the prostate gland, integrated this with the recent advances in the knowledge of prostatic malignancy and proposed a hypothesis for rational therapy of cancer of this gland. The work of Kutscher and Wolbergs, the Gutmans and Gomori all pointed to the fact that a characteristic of normal, adult prostatic epithelium was the secretion of acid phosphatase. This, coupled with the observations that the enzyme was present in cancerous prostatic epithelium in the primary tumor and also in metastases[141] together with the elevated serum acid phosphatase level, led to the conclusion that many carcinomas of the prostate are composed of adult epithelial cells. On the basis of previous observations that mature prostatic epithelium undergoes atrophy when normal androgen production is sharply decreased by castration or physiologically inactivated by estrogen administration, Huggins and his associates postulated that

significant clinical improvement should occur following bilateral orchiectomy in patients with far advanced prostatic carcinoma.[139,140] Since this hypothesis could not be explored in experimental animals, it was tested by clinical trial.

In patients with far advanced prostatic carcinoma with metastases to bones Huggins and his co-workers followed changes in the serum acid and alkaline phosphatase concentrations as well as the clinical condition of the patient. The alkaline phosphatase proved to be a valuable objective measurement of alteration of the tumor because it provided an indication under these conditions of osteoblastic activity at the site of carcinoma metastases.[141] It was demonstrated that following castration and/or administration of estrogens the serum acid phosphatase fell abruptly and there was clinical improvement. The alkaline phosphatase remained elevated for a longer time and returned to normal levels gradually. It was also possible to show that administration of androgen caused an elevation of the serum acid phosphatase concentration and clinical deterioration. These human experiments, therefore, appeared to confirm the thesis proposed and also offered promise of effective therapy for a common and devastating malignant disease.

Mechanism of Action. There are two subjects to be considered in this section: (1) the mechanisms involved in controlling the effects of androgen in the male by the administration of estrogen and (2) the effect of androgen deprivation on carcinomatous prostatic epithelium.

Normal function of the germinal epithelium and the interstitial cells (site of hormone elaboration) of the testis is dependent upon pituitary gonadotropins. Smith and Engle in a series of classical experiments[142] demonstrated that ablation of the hypophysis in the male adult animal was followed by profound testicular damage. Characteristically, there were loss of gametogenic activity and changes in the accessory sex organs comparable to those seen in a castrate animal. Moore and Price[143] produced a similar alteration in the morphology and function of the testes in normal animals by administration of estrogen. The deleterious effects of estrogen did not appear if a gonadotropic extract was injected simultaneously with the gonadal hormone. From evidence of this nature it has been concluded that estrogen does not have a harmful effect on the testes directly but inhibits the secretion of gonadotropic hormones by the pituitary gland, with the result that the gonads become atrophic.

In addition to the indirect mechanism Huggins presented evidence which would indicate that estrogen nullifies the action of testosterone by direct antagonism at the peripheral end organ.[144] It is to be noted that most of the evidence from animal experimentation is against the hypothesis that there is a direct antagonism between estrogen and androgen on specific cells. However, Huggins' observations in the castrate dog and studies in castrate men provide circumstantial evidence that in the case of prostatic epithelium estrogen acts peripherally and its effects are opposite to those of androgen.

Thus, the mechanism whereby estrogen impedes the growth of prostatic carcinoma or even causes it to regress is (1) through inhibition of pituitary function which in turn depresses the secretion of testosterone by the interstitial cells of the testis and (2) by direct antagonism of the action of testosterone on prostatic epithelium. Less clear is the mechanism of action of estrogens against prostatic carcinoma after castration. Theoretically, depression of adrenal androgen production could explain the salutary effects sometimes noted when estrogen therapy is administered to previously castrated patients. Assays of urinary hormone levels (gonadotropins and 17 ketosteroids) reported by Dean[145] suggested that estrogens decreased androgenic steroids by an indirect effect on the pituitary or by a direct action on the adrenal cortex. Clinically, however, this worker could not demonstrate that stilbestrol therapy was

effective after castration relapse in his patients. Other investigators have found that further beneficial effect may occur with estrogen therapy when a remission induced by orchiectomy is ended.

It now becomes necessary to inquire into the mechanism of action of testosterone on the prostatic epithelium in order to understand the fundamentals of androgen control therapy of prostatic carcinoma. Little is known about the immediate action of hormones on cellular physiology. In fact, the only precise information of this nature concerns the action of insulin in carbohydrate metabolism.[146] Although such detailed knowledge of the action of testosterone on prostatic epithelium is not available, Barron and Huggins have made observations of great interest and possible significance.[147] They studied, *in vitro*, the carbohydrate metabolism of prostatic epithelium obtained from dogs before and after castration or diethylstilbestrol administration. The oxidative phase of metabolism was characterized by determining the oxygen consumption in the presence of glucose and pyruvate. The anaerobic phase was studied by determining glucose fermentation under optimum conditions for glycolysis. Their experiments showed that when the prostate was deprived of androgen support there was a marked decrease in the oxidative phase of carbohydrate metabolism as indicated by a diminished Q_{oxygen} and $Q_{pyruvate}$. No change was noted in the anaerobic phase of carbohydrate metabolism. Although these observations do not specifically explain the action of testosterone, they indicate the fundamental role played by this hormone in the cellular physiology of prostatic epithelium.

Clinical Application. Since the first reports by Huggins[139,140] on the effect of orchiectomy and of Herbst[148] on use of estrogens in the therapy of prostatic carcinoma, there have been many publications which have confirmed the beneficial action of androgen control on the disease.[149–160] From these articles and many others it is possible to make some general statements about the immediate results to be anticipated in those patients responding satisfactorily. From the patient's viewpoint the most dramatic effect is relief of pain. Associated with this there is a sense of well being, an increased appetite and a gain in weight. Frequently the anemia associated with far advanced disease will respond to iron therapy. Objectively, the serum acid phosphatase usually drops to normal levels; the alkaline phosphatase may first rise, then gradually fall; soft tissue metastases regress and in some instances there is evidence of healing of bone metastases. In most patients there is evidence by rectal palpation of decrease in size of the primary tumor with attendant relief of obstructive urinary signs and symptoms. Neurologic symptoms due to pressure or traction on nerve roots, particularly the cauda equina, are also relieved. Serial biopsy studies by Fergusson[153] and by Schenken et al.[161] revealed alterations in the nuclei of the epithelial cells, consisting of reduction in size, progressive condensation of the chromatin, loss of nucleoli, loss of mitotic figures and pyknosis. The cytoplasmic changes consisted of progressive vacuolization and finally rupture of the cell membrane. After some months most of the malignant tissue was replaced by scar tissue. Significantly, however, it was noted that there never was complete disappearance of malignant cells. Dean mentions[145] one patient with histologically proven prostatic carcinoma who died a cardiac death four years after institution of androgen control therapy. Despite careful autopsy study no microscopic evidence of residual cancer was disclosed in this man. This observation may indicate that an occasional cure will result from androgen control therapy.

As has been indicated not every case of prostatic carcinoma responds satisfactorily to androgen control therapy. Huggins has suggested that the explanation for this is related to the cellular characteristics of the malignancy. The anaplastic epithelial tumor does not, in his opinion, react to androgen withdrawal as does adenocarcinoma. This

would be in keeping with the thesis that adenocarcinoma is made up of mature epithelial cells and therefore responds in a manner analogous to normal epithelium whereas the undifferentiated type of carcinoma is not subject to hormonal influences. This explanation has both adherents and antagonists, i.e., those who have found that the cell type is not a determining feature in the response to therapy.

There are many other questions of a practical nature which will require additional experience to answer definitely. At present, for example, it is impossible to state unequivocally that castration is superior to estrogen therapy or the reverse, or that a combination of orchiectomy and estrogen is the best therapeutic regimen. Most urologists utilize both means for decreasing androgen, but there is considerable disagreement on the order in which the two procedures should be carried out. It is generally agreed that castration results in a more rapid remission of signs and symptoms but there is a surgical risk involved, particularly in the debilitated patient, and the psychologic barrier to castration is important in some instances. Following castration, there may be symptoms of vasomotor instability in the form of hot flushes and sweating, but these can be controlled easily by estrogens. Administration of estradiol or synthetic estrogens also results in toxic manifestations in some instances. One of these is gastrointestinal upsets, particularly with use of stilbestrol. Most troublesome is enlargement and tenderness of the breast due to the action of estrogen on the ductal epithelium.[162,163]

Following introduction of androgen control therapy for prostatic cancer, there was a wave of intense enthusiasm as a result of the dramatic immediate responses and hopes ran high that a cure for this type of malignancy had been found. A sufficient time interval has now passed to assess the results of therapy and a very much more restrained attitude must be taken. In Table II the results of therapy of several series of patients who have been observed for two years or more are summarized. The statistics of the control series are valid for comparison with the specific therapy series because the patients were treated surgically for relief of urinary obstruction and also were treated with sulfonamides for urinary tract infections when indicated. These are important supportive measures in prolonging life in prostatic malignancy as can be demonstrated easily by comparing the mortality figures for this control series of patients with those obtained by others before the general employment of transurethral surgery and bacterial chemotherapy.[168] It is evident from the data in Table II that androgen control therapy of prostatic cancer has significantly prolonged life. For example, in the control series 62 per cent of the patients died one year after there was evidence of dissemination of the malignancy from the primary site, whereas the statistics of the several treated series indicate that only about 40 per cent of the patients were dead after one year. However, it is also to be noted that as the period of observation lengthens, the mortality figures in the treated series more closely approach the control values.

The explanation for development of refractoriness to androgen control therapy in prostatic malignancy is not yet known although it has been suggested that one of the causes may be a change of the malignant cell from a mature prostatic epithelial cell to a less well differentiated, more anaplastic type. Of interest in this regard is the observation[169] that adenocarcinoma cells of the human prostate, cultivated in the anterior chamber of guinea pig eyes, lose their power to produce acid phosphatase, yet after serial transplantation through several rodent hosts they maintain their typical microscopic appearance and malignant characteristics. These findings would point to the fact that de-differentiation of cell type can and does take place in this neoplasm.

Comment. To date androgen control therapy of prostatic cancer has provided the single, most outstanding, practical con-

tribution to the chemotherapy of malignancy. It can be stated unequivocally that castration and/or estrogen administration should constitute a part of the routine therapeutic management of all cases of disseminated carcinoma of the prostate gland.

SEX HORMONES IN THE THERAPY OF CARCINOMA OF THE BREAST

Background and Rationale. The existence of a relationship of the ovarian hormones to cancer of the breast was first clearly demonstrated by Leo Loeb and his associates. They found that the incidence of spontaneous carcinoma of the breast in mice was significantly decreased by castration.[170,171] The importance of the stimulative action of estrogen on the development of carcinoma of the breast was brilliantly demonstrated experimentally by Lacassagne.[172] Using a strain of mice in which 72 per cent of the females characteristically succumb to adenocarcinoma of the breast but in which no males develop spontaneous breast tumors, he administered estrone to the latter over prolonged periods. Initially, a network of ducts developed in the axillary and inguinal

TABLE II
ANDROGEN CONTROL THERAPY OF PROSTATIC MALIGNANCY

Authors	Control (Vest and Frazier)		Vest and Frazier		Huggins		Alyea		Emmett and Greene		Nesbit and Plumb		Herger and Sauer	
No. of Patients	74		74		20		37		133		75		109	
Months after Onset of Rx	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive
0– 6	20	80	5	95	..	..	5	95	13	87	8	92	16	84
6–12	38	62	14	86	20	80	16	84	24	76	19	81	28	72
12–18	57	43	19	81	..	..	33	67	42	58	29	71	40	60
18–24	62	38	28	72	55	45	35	65	45	55	37	63	49	51
24–30	66	34	37	63	..	..	..	..	..	..	43	57	60	40
30–36	69	31	42	58	..	..	..	..	..	..	54	46	67	33
36–42	69	31	43	57	..	..	..	..	..	..	61	39	73	27
42–48	73	27	..	..	65	35	..	..	..	..	67	33	74	26
48–54	76	24	..	..	..	..	..	..	..	..	..	..	74	26
54–60	77	23	..	..	75	25								
60–72	80	20												
72–84	82	18												

Vest and Frazier, *J. Urol.*, 56: 97, 1945.
Huggins, *J. A. M. A.*, 127: 63, 1945.
Alyea, *J. Urol.*, 53: 143, 1945.
Emmett and Greene, *J. A. M. A.*, 127: 63, 1945.
Nesbit and Plumb, *Surgery*, 20: 263, 1946.
Herger and Sauer, *New York State J. Med.*, 47: 494, 1947.

In addition to the tremendously significant advance in practical therapeutics this type of treatment has greatly stimulated laboratory investigation of cancer chemotherapy. The results have demonstrated the effectiveness of alteration of the internal environment in retarding the neoplastic growth of prostatic epithelium. It is possible that other changes in the internal environment which are compatible with function of the normal cells of the host may be incompatible with the existence or growth of other types of neoplastic cells.

regions of the treated males. This was followed by proliferation of the ductal epithelium and, between the fourth and tenth months, a rapidly growing adenocarcinoma evolved from which the animals died, either with ulceration of the tumor through the skin or with pulmonary metastases. Even more impressive were Lacassagne's experimental results in which estrogen carcinogenesis was demonstrated in a strain of mice in which the incidence of spontaneous carcinoma of the breast was very low. In these experiments after twelve to eighteen months of estrogen administration all of the mice died with malignant tumors of the breast. As a result of these observations Lacassagne suggested the possibility that antagonism of estrogen by androgen might provide a significant therapeutic advance in the treatment of human mammary cancer.

This suggestion was tested experimentally in mice[173–175] and it was found that the male sex hormone, testosterone, indeed could prevent the appearance of breast cancer in strains in which spontaneous mammary carcinoma incidence was high. However, it is to be noted that the experiments were conducted by administering the androgen very shortly after the birth of the animals and continuing it over long periods. Under these conditions the ovary never became functional and the breasts of the female mice remained rudimentary. Loeser[176] delayed androgen therapy until later in the life of the mice and found that if the treatment was instituted only shortly before the expected appearance of the malignancy no protection was afforded.

Although the experimental evidence of an inhibitory effect of androgen on either the development or growth of carcinoma of the breast was not convincing, there were scattered clinical trials of this form of therapy in inoperable breast cancer in humans. Ulrich,[177] Loeser[176] and Fels[178] reported encouraging results in a few patients. Marked impetus to use of androgen therapy in far advanced carcinoma of the breast has been provided by a series of reports by Adair and Herrmann in the past two years. These will be discussed in detail in the section on clinical application.

Mechanism of Action. In order to understand the mechanisms by which androgenic hormone could conceivably retard the progress of cancer of the breast it is necessary to review briefly the endocrine factors which influence the histology and physiology of the mammary gland.

Ovarian Hormones: The importance of estrogenic follicular hormone in the development and function of the breast has been clearly established by many observations, both experimental and clinical.[179,180] It now is generally accepted that in the human, proliferation of the duct systems and growth of the connective tissue framework of the breast is dependent upon the estrogenic hormone. Progesterone, the hormone of the corpus luteum, is necessary for the development of the alveoli and lobules of the breast. Under the influence of progesterone, after the breast has first been prepared by estrogen, the epithelium is converted to the typical secretory type. It is important to note, however, that although histologically the gland looks like a secretory organ following estrogen plus progesterone administration, lactation cannot be induced by these hormones alone.[181]

Hormones of the Pituitary Gland: A specific lactogenic hormone, prolactin, has been isolated from the anterior hypophysis. This induces lactation in the experimental animal after the breast has been suitably stimulated by estrogen and progesterone.[182] Thus, it is apparent that a delicate and rather intricate balancing of the hormones of the pituitary and ovaries is essential for normal function of the mammary gland.

It has been reported that there is another hormone from the anterior pituitary, mammogen, which is essential for the development and growth of the breast.[183] However, the experimental evidence for this additional component of the anterior pituitary hormone is not convincing and more recent work with highly purified prolactin indi-

cates that this fraction alone can reproduce all of the experimental observations attributed to mammogen.[184]

Hormones of the Adrenal Cortex: In addition to the corticosteroids which have very significant physiologic functions in modifying electrolyte, protein and carbohydrate metabolism, estrogenic and androgenic hormones have been isolated from the adrenal glands.[185] The extent to which the adrenal cortical sex steroids influence the reproductive system under normal conditions is not known. However, it is important to appreciate that after castration the sex hormones continue to be excreted in the urine in appreciable amounts, indicating that the adrenal cortex is able to secrete significant quantities of these hormones.

With this background of information on the hormones which influence the breast and their sites of elaboration, the mechanisms whereby androgenic hormone could antagonize the physiologic actions of other hormones may be considered. As has been discussed in the section on use of estrogens in prostatic malignancy there is a reciprocal relationship between the gonadotropins of the pituitary and the hormones of the gonads. Thus, theoretically, it would be anticipated that suitable doses of androgenic hormone would depress pituitary activity and secondarily inhibit the physiologic function of the gonads. It had been shown that administration of testosterone to women decreases the urinary excretion of pituitary gonadotropins and coincidently there is evidence of suppression of ovarian function.[186] Not only is the elaboration of gonadotrophic hormones of the pituitary diminished by excessive gonadal hormone administration, but also all of the other secretions of the hypophysis are depressed. If adrenotrophic hormone from the pituitary is decreased, the release of sex steroids by the adrenal cortex is concomitantly lowered as Long and his collaborators have shown.[187]

There also are both experimental and clinical observations which suggest that androgen may peripherally antagonize the effects of estrogen. Thus, Shorr and his associates[188] have shown that the cornifying action of estrogen on the vaginal epithelium of postmenopausal women can be reversed by simultaneous administration of testosterone. The experiments of Robson[189] on ovariectomized mice, in which vaginal cornification by estrogen was prevented by concomitant administration of androgen, also indicate a peripheral neutralizing action of testosterone. It is to be noted, however, that the evidence for a direct peripheral antagonism of the sex hormones is subject to question inasmuch as the contribution of the adrenal sex steroids has not been controlled in these experiments. There is circumstantial evidence indicating that a minute amount of progesterone is necessary for the complete response of estrogen in an appropriate end organ. It has been shown that progesterone is elaborated by the adrenal cortex, and it is presumed that it is this source of progesterone which makes possible the evident complete replacement of the follicular hormone by synthetic estrogens after ovariectomy. In experimental animals such as the hamster, in which no progesterone is elaborated by the adrenal cortex, it is impossible to duplicate the characteristics of estrus by estrogen administration after castration. Thus, the experiments which purport to demonstrate a peripheral antagonism of estrogen and androgen may, in fact, conceivably be another manifestation of pituitary inhibition in which the adrenotrophic hormone is suppressed.

In addition to the antagonism of estrogen by androgen it is necessary to consider another physiologic action of testosterone which may be significant in understanding the results of therapy with this hormone in breast malignancy. Albright,[190,191] Kenyon,[192] Abels et al.[193] and others have shown that testosterone affects protein metabolism in man. From their observations that administration of the hormone is followed by a positive nitrogen balance without elevation of the serum non-protein nitrogen they concluded that protein anabolism is stimulated or protein catabolism is in-

hibited. It has also been shown that testosterone induces a positive calcium balance. Albright presents an attractive hypothesis in which the mechanism of this observation is ascribed to increased osteoblastic activity with deposition of calcium in bone.[190]

Clinical Application. Androgen: Metastases from carcinoma of the breast may be limited to the soft tissue or to the skeletal system or they may involve both soft tissue and bone. As will be seen in the following comments the localization of metastatic carcinoma of the breast appears to be a significant factor in the response to chemotherapy.

In 1942 Farrow and Woodard[194] reported a carefully observed series of thirty-three patients with bony metastases who received testosterone propionate in doses of 5 to 25 mg. on six to twelve occasions. Their results were, on the whole, discouraging and in fact they presented evidence which indicated that in some instances the progress of the neoplasm was accelerated. However, in 1946 Herrmann and Adair[195] published results of androgen therapy of metastatic breast carcinoma which were more encouraging. To date Adair and his associates have reported twenty-seven cases of patients with advanced carcinoma of the breast treated with testosterone propionate, giving data in sufficient detail for tabulation of results.[195–197] In later communications Adair stated that 450 patients had been so treated but gave no details.[198,199] Preliminary reports by Schwander and Marvin,[200] Jones[201] and Davison and Letton[202] substantially confirm the observations of the Memorial Hospital group.

At the present time the recommended dosage of testosterone propionate is 100 mg. by intramuscular injection three times weekly for a period of eight to ten weeks. This total dosage of 2,400 to 3,000 mg. is far in excess of that employed by Farrow and Woodard and may be significant in explaining the difference in clinical response noted by the two groups.

Table III presents a brief summary of the results of androgen therapy in the twenty-seven cases reported by Adair and his associates. The pertinent facts were abstracted from the published case histories. As can be seen testosterone is rarely efficacious in the control of soft tissue metastases of carcinoma of the breast and the course of the lesion is not altered. However, of the fifteen patients with osseous involvement by the malignancy, only two patients failed to receive any benefit. In the remaining thirteen individuals the pain produced by the bone metastases was relieved and there was a feeling of well being. Occasionally, there was roentgen evidence of bone healing, however, this was only temporary. Whether or not life has been significantly prolonged in the patients with osseous metastases is difficult to state. Reference to the table shows that in ten of these fifteen patients there was either marked dissemination of the disease in the osseous system or the appearance of soft tissue metastases. In the latter group it would be anticipated that death would occur within one year.

Associated with the relief of bone pain following testosterone therapy, there are changes in the blood chemistry which are of importance in evaluating the success of therapy in the presence of osseous metastases. The serum calcium is usually elevated above the normal concentration. Following administration of androgen, the calcium level drops toward normal. This is interpreted as evidence of deposition of calcium in new bone. In two of the reported cases the calcium concentration rose following testosterone, with mild symptoms of calcium intoxication; x-ray examination of the metastatic lesions in the bones revealed progression in both instances. It therefore may be concluded that a significant elevation of the calcium level during testosterone treatment is an indication to discontinue therapy as it is probable that the malignant cells are being stimulated rather than depressed. In the majority of successfully treated patients the serum alkaline phosphatase rose as the calcium fell, indicating increased osteoblastic activity. In these patients there was also a gain in weight up to almost 10 Kg. which was promptly lost

when the therapy was discontinued. This probably is largely due to the effect of testosterone on nitrogen retention rather than an expression of increased caloric intake since it did not persist even though the patient remained asymptomatic and the caloric intake remained constant.

The side effects of testosterone consisted of hirsutism, acne vulgaris, deepening of the voice, suppression of menstruation and increased libido with enlargement of the clitoris. None of these masculinizing effects necessitated discontinuance of the drug.

Estrogen: Estrogenic therapy of carcinoma of the breast has also been reported. The proposed rationale is highly speculative, and is perhaps most significant as an expression of the great need for better understanding of the biology of this disease. From the fact that the incidence of malignant tumors of the breast is high between the ages of forty and sixty years and the fact that this is also the age range in which the incidence of menopause is highest the following hypothesis has been set forth:[203] With the onset of the climacterium, there is either atrophy

TABLE III

RESULTS OF ANDROGEN THERAPY IN TWENTY-SEVEN PATIENTS WITH METASTATIC CARCINOMA OF THE BREAST

Case No.*	Age	Evident Distribution of Disease	Duration of Remission (months)	Remarks
1A	63	Soft tissue	5	Died of disease nine months after institution of therapy
Not given		Soft tissue	0	Died with pulmonary metastases without response
Not given		Soft tissue	0	Died with liver metastases without response
Not given		Soft tissue	0	Died of disease; no response to therapy
Not given		Soft tissue	0	Died of disease; no response to therapy
Not given		Soft tissue	0	Died of disease; no response to therapy
1B	39	Soft tissue	0	Living one year after onset of therapy; disease constantly progressive
2B	56	Soft tissue	0	Terminal six months after institution of therapy
3B	54	Soft tissue	0	Living fifteen months after onset of androgen therapy; lesion controlled by x-ray
4B	52	Soft tissue	0	Living two months after institution of androgen therapy; lesion progressive
5B	40	Soft tissue	0	Living three months after institution of androgen therapy; no improvement
6B	27	Soft tissue	3.5	No further follow-up report
2A	47	Osseous	5	Evidence of cerebral metastases plus pulmonary metastases developed; terminal eight months after institution of androgen therapy; no recurrence of bone metastases
3A	42	Osseous and soft tissue	9	Terminal thirteen months after institution of androgen therapy with widespread osteolytic lesions of bone
4A	44	Osseous	18	Asymptomatic at last report; has received repeated courses of androgen therapy
Not given		Osseous	0	Calcium intoxication and rapid progression of osteolytic lesions
1C	60	Osseous	8	Asymptomatic at last report
2C	59	Osseous	6	Asymptomatic at last report
3C	59	Osseous	6	Asymptomatic at last report
4C	43	Osseous	3	Asymptomatic at last report
5C	58	Osseous	6	Asymptomatic at last report but evidence of progression of metastatic lesions
6C	40	Osseous	7	Asymptomatic at last report; progression of osteoblastic metastases
7C	45	Osseous	4	Pulmonary metastases appeared at this time; no follow-up
8C	55	Osseous and soft tissue	1	Progression of pulmonary metastases
9C	39	Osseous	1	Terminal four months after institution of androgen therapy, with evidence of progression of bone metastases
10C	62	Osseous	0	Died two months after institution of therapy
11C	53	Osseous	5	Evidence of liver metastases at this time

* The letters after the case numbers refer to the source of the information. A,[195]; B[196]; C, [197].

or dysfunction of the ovaries with an oversecretion of hormones of the anterior pituitary (follicle-stimulating hormone, luteinizing hormone and prolactin) and concomitantly there is an alteration in the cellular activity of breast tissue. An imbalance develops between the various endocrine glands resulting in thyroid hypo- or hyperactivity and possibly in hyperactivity of the suprarenal cortex. The cellular activity of the breast, no longer under the control of ovarian hormones and possibly stimulated by other hormones, becomes abnormal and in certain instances frank malignancy develops. Thus, the replacement of estrogenic hormone by restoring the normal hormone balance might provide an environment in which the malignant cells are unable to survive.

An alternate rationale for the use of estrogens in carcinoma of the breast has been suggested by the observation of Haddow that carcinogenic hydrocarbons under certain conditions possess the property of retarding the growth of normal and malignant tissue in experimental animals.[204] On the assumption that estrogens are significant in the etiology of human carcinoma of the breast they theoretically might also retard the growth of the tumor.

These hypotheses have been put to clinical test in a number of patients and the result in more than 300 cases have been reported in the literature. In a symposium on the subject[205] ten British observers pooled their experience with 168 patients. Of these, one hundred were less than and sixty-eight were over sixty years of age. Although detailed reports are not available, it may be inferred from the discussion that under the age of sixty, estrogen therapy accelerated the progress of malignancy and was therefore definitely contraindicated; in patients over sixty there was regression of the soft tissue metastases and of the primary tumor in approximately 50 per cent of the cases. There is no follow-up report on these patients so that it is impossible to make any statement about the effect of estrogen therapy on prolongation of life. Haddow and his associates,[206] Nathanson[207] and Herrmann et al.[208] also have treated patients with synthetic and natural estrogens with similar results.

Comment. From the evidence presented it may be concluded that large doses of androgenic hormone will provide relief of pain and a subjective sense of well being in patients with carcinoma of the breast metastatic to bone. Although objective x-ray evidence of bone healing is rarely seen, there frequently are changes in the blood chemistry which would indicate that reparative processes in the bone are occurring. In any event it is apparent that the therapy provides only temporary palliation.

The possible mechanisms for the observed effects of androgens in carcinoma of the breast have been discussed. In view of the marked difference in the clinical response to androgen therapy depending upon the localization of the metastases it is questionable whether antagonism of estrogen by testosterone plays any significant part in the results. It is difficult to believe that antagonism of estrogen would be effective in retarding neoplastic growth in the bone but be ineffective when the same neoplasm was growing in soft tissues. A more acceptable explanation for the observed effects of testosterone therapy of breast cancer may be derived from the known changes in protein and calcium metabolism produced by this hormone. The fact that responses are limited to those patients with osseous metastases is then more understandable.

Radiotherapy has been employed effectively in the palliation of metastatic breast carcinoma to the bones and with less regular success in the soft tissue metastases for a long period of time.[1] Since this is so, it may justifiably be asked why androgen therapy should be considered. There are at least three situations in which this form of chemotherapy of inoperable carcimona of the breast with osseous metastases is indicated: (1) when radiotherapy is not available, (2) when the dissemination of symptomatic metastatic lesions in the

skeletal system is so great that radiotherapy is not practical and (3) when it is no longer permissible to employ radiotherapy because the pain has not responded to x-ray treatment, the tumor has become refractory to x-ray or the skin overlying the involved area cannot withstand further radiation.

Estrogen therapy of carcinoma of the breast should be reserved for patients who are well past the menopause and who have radioresistant soft tissue metastases. Under these conditions estrogens may be employed as a last resort. It is necessary to observe the patient closely during therapy so that the drug can be discontinued with the first evidence that the neoplasm is being stimulated rather than depressed.

NITROGEN MUSTARD

Background and Rationale. The emergence of nitrogen mustard as a significant chemotherapeutic agent against malignancy is a fascinating and dramatic story. The development of nitrogen mustard is inextricably linked to the World War I vesicant agent, "mustard gas." Dichloroethyl sulfide, popularly known as yellow cross gas, Lost and Yperite as well as mustard gas, was first prepared by Richie in 1854, independently synthesized by Gutherie and Niemann in 1860 and fully described both chemically and physiologically by Victor Meyer in 1886.[209] These chemists appreciated the highly toxic actions of the compound and Meyer noted that even more striking than its vesicant properties was its lethal action in small doses when administered parenterally.

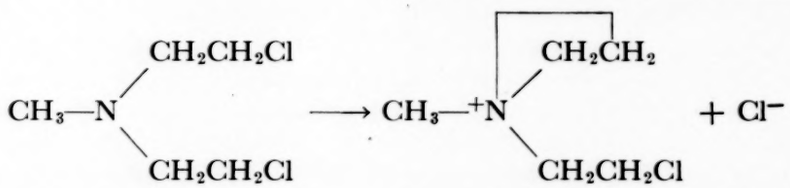
During the spring of 1917 the Germans carried out secret field tests with such satisfactory results that they adopted dichloroethyl sulfide as an artillery-shell filling and accumulated a large quantity of these (yellow cross) shells before the Allies were aware of this development. On the night of July 12, 1917, the Germans loosed an artillery bombardment against the British front near Ypres in Flanders. An indication of the devastating effect produced by this agent is given in the statistics of the first three weeks of mustard gas use. Fourteen thousand, two hundred seventy six cases of gas-shell poisoning were admitted to the British casualty stations and about 500 deaths occurred among these patients.[210]

Descriptions of mustard gas intoxication soon appeared in the medical literature. At first attention was focused on the local actions as manifested by skin vesication which frequently progressed to deep ulcers, conjunctivitis, photophobia and lacrimation, irritative laryngitis, bronchitis with intractable cough, aphonia and often secondary bronchopneumonia.[211,212] Somewhat later, however, it was appreciated that serious systemic toxicity was not uncommon, and the Krumbhaars called attention to the characteristic finding of leukopenia in the fatal cases due to marked depression of the bone marrow function.[213] Laboratory studies were carried out in order to define the mechanism of action of dichloroethyl sulfide, and by the termination of the war the hypothesis of Lynch, Smith and Marshall[214] was largely accepted. These workers believed that the lipoid solubility of the compound facilitated its localization in the cell. At this site hydrolysis took place with the liberation of hydrochloric acid thereby producing a cytotoxic effect.

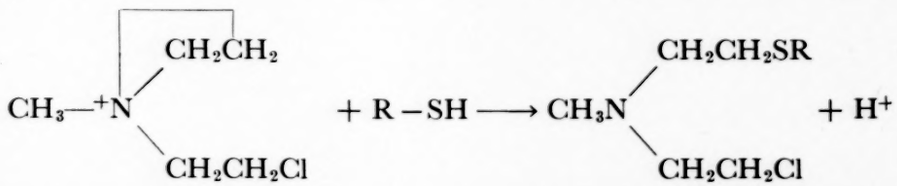
In the interim between World Wars I and II there was continued activity in the chemical warfare laboratories of the French and Germans. By the time the United States entered the war it was known that the enemy had available, in addition to dichloroethyl sulfide and other potential chemical warfare agents, the nitrogen analogs of mustard gas, the so-called nitrogen mustards. The Allies strongly believed that advances in the treatment of gas casualties could be made only when the mechanism of action of the toxic agents was better understood. To this end chemical, physiologic and pharmacologic studies were initiated in university and government laboratories. Observations on the biologic actions of nitrogen mustards were greatly facilitated by the fact that crystalline hydrochloride salts of these compounds could be

prepared. Gilman and Philips have summarized the pharmacology of the nitrogen mustards.[215] Clinical applications of these compounds in the therapy of malignant lymphomas was suggested by the susceptibility of lymphoid tissue to the cytotoxic action of the nitrogen mustards in sublethal doses.

Mechanism of Action. A clear understanding of the pharmacologic actions of nitrogen mustards depended upon clarification of the chemistry of the compounds.[216-230] Stein, Fruton, Stahmann, Bergmann and Golumbic demonstrated in a series of experiments that the stable, crystalline nitrogen mustards and sulfur mustard undergo transformation to a cyclic onium cation when they are put into solution at the pH of body fluids, with the liberation of Cl^- which is highly reactive chemically. This ring formation, using methyl bis (β-chloroethyl) amine (the nitrogen mustard most widely used therapeutically) as the example, may be thus illustrated:



It was quickly appreciated that the biologic activity of the nitrogen mustards was dependent upon the ring form which reacted avidly with a great variety of functional groups of compounds with physiologic significance. For example, the reaction of the ethylene immonium cation with compounds having sulfhydril groups may be diagrammed:



Many pharmacologic actions of the nitrogen mustards have been described, these depending upon the dose administered.[215,231-242] Comments, however, will be limited to the biologic effects produced with doses comparable to those in human therapy. Under these conditions the outstanding actions of the drug are reflected in the response of hemopoietic tissue and the gastrointestinal tract.[237-239] After intravenous administration to a normal dog there is a latent period of one-half to one hour during which the animal appears entirely unaffected. The dog then begins to salivate and this is quickly followed by vomiting. The vomiting may continue intermittently for a period of several hours. The mechanism of the emesis is presumed to be a reflex initiated in the gastrointestinal tract because as the dose of nitrogen mustard is increased the gastrointestinal symptoms become more severe with protracted vomiting, diarrhea and histologic evidence of hemorrhagic necrosis of the gut epithelium. Within twenty-four hours after the injection of nitrogen mustard the leukocytes of the peripheral blood begin to decrease and a differential examination reveals a relative lymphocytopenia. In the next few days there is further depression of the white blood count and granulocytopenia develops. The bone marrow at this time is hypoplastic with a decrease of all elements and the lymphoid tissue of the body shows widespread destruction. With these doses, thrombocytopenia is inconstantly present and anemia is not observed for several weeks, if at all, probably due to the longer life span of erythrocytes as compared with other cells. At this dosage level the depression of hemopoiesis is reversible and within

three weeks the bone marrow and peripheral blood picture are normal.

The site of cellular action of the nitrogen mustards has been localized in the nucleus. In a fascinating series of experiments Bodenstein and Gillette have observed the morphologic changes in embryonic cells exposed to low concentrations of the drug.[243,244] Directing their attention especially to the exposed ectoderm of Amblystoma punctatum they noted that all mitotic activity had come to a standstill forty-eight hours after exposure to nitrogen mustard. The cells were arrested in the interphase state of their mitotic cycle. However, the nuclei of these cells continued to grow, attained a giant size and ultimately broke down into a number of roundish fragments. Friedenwald and his colleagues studied the cellular changes induced by nitrogen and sulfur mustard in adult tissue.[245,246] Their test object was the corneal epithelium of the rat. Exposing the eye to very dilute solutions of the mustards, they also observed nuclear fragmentation and death of the cell. They concluded that this phenomenon was a form of pathologic mitosis. Friedenwald reported that death of the corneal epithelium, characterized by karyolysis and by pyknosis, was produced by progressively increasing the dose of mustards.

That the mustards can affect the most intimate physiologic mechanisms of the cell nucleus is shown by the experiments of Auerbach, Robson and Carr. These investigators exposed the fruitfly, Drosophila melanogaster, to low concentrations of sulfur mustard and observed striking chromosomal alterations as manifested by increased incidence of sex-linked lethal genes and chromosomal transformations.[247,248] Stahmann and Stauffer[249] induced mutants in Penicillium notatum by exposing the spores to nitrogen mustards, and Horowitz and his associates produced mutations chemically in Neurospora crassa.[250] In all of these investigations the effects of the mustards on chromosomes were compared with those produced by radiant energy and these were found very similar quantitatively and qualitatively.

It has been repeatedly noted by the investigators who have studied the biologic actions of the mustards that these chemicals mimic the effects of x-ray and ultraviolet radiation to a remarkable degree.[246,251,252] It is possible that a clear understanding of the mechanism of action of the mustards will also provide some insight into the mechanisms whereby radiant energy produces its effects on cells.

Clinical Application. Following the pharmacologic observations on the cytotoxic effects of the nitrogen mustards (bis and tris (β-chloroethyl) amines) on a variety of histologic cell types, Goodman, Gilman and their associates and Jacobson and his colleagues initiated therapeutic trials with these drugs in humans.[253,259] Striking results in neoplasia of the lymphatic and hemopoietic systems prompted a more extensive study under the direction of the committee on Growth of the National Research Council. It would be premature to draw final conclusions regarding the chemotherapeutic efficacy of the nitrogen mustard compounds used clinically thus far or to assume that related compounds with a higher selectivity of action for neoplastic tissue will not be forthcoming. Attention should be called to the fact that no cures have been reported in any of the numerous types of disease processes in which these drugs have been used and it should be stressed that therapy with nitrogen mustards (abbreviated HN) therefore remains only palliative in nature.

Administration. Because of the high incidence of phlebothrombosis at the injection site and the quantitatively greater leukopenia following its use, as well as the failure to demonstrate superior clinical results to those seen with the methyl bis (β-chloroethyl) amine (HN_2), the tris (β-chloroethyl) amine (HN_3) has been largely discarded as a therapeutic agent in favor of HN_2. Most clinical reports deal with results obtained with this latter drug although observations on new compounds are being made.[254] HN_2 is dispensed in sterile bot-

tles containing 10 mg. of the drug as the hydrochloride. In clinical practice the crystalline material is dissolved by the addition of 10 cc. of sterile 0.9 per cent saline to the bottle, the calculated dose is withdrawn in a sterile syringe and injected within five minutes after mixing into the rubber tubing of a rapidly running intravenous infusion. The commonly employed dosage schedule is 0.1 mg. of HN_2 per Kg. of body weight daily for four days, giving a total of 0.4 mg. per Kg. of body weight per course of therapy. Variations of this schedule can be utilized, such as 0.2 mg. per Kg. of body weight on two successive days; or one can use either of these dosage schedules with rest days between successive doses in the case of debilitated or frail patients. Neoplasms rarely are susceptible to doses as small as 0.04 mg. per Kg. of body weight.[255] Because of the narrow margin between the therapeutic and toxic ranges, doses in excess of those mentioned are hazardous.[256] Hypnotic doses of barbiturate compounds administered an hour before and immediately after each treatment frequently diminish nausea and vomiting following drug injection. Other measures such as pyridoxine and antispasmodics have not significantly alleviated these toxic side reactions. Subsequent courses of therapy should be undertaken only after careful evaluation of the response of the bone marrow and neoplastic process to the initial course of treatment. Spurr has stated that six weeks should elapse between courses[260] while others[258] wait only two weeks in some cases before resuming mustard therapy.

The decision as to whether patients should be hospitalized for treatment depends largely on their general state of health, the extent of the neoplastic or other disease process to be treated, and the clinical facilities available. Suffice it to say that therapy should be assiduously supervised and post-treatment observation for signs of drug toxicity should be insured. In most clinics careful check on the peripheral blood picture is made frequently, beginning several days after the completion of a course of therapy until marrow regeneration is nearing completion (usually two, occasionally three weeks later). Follow-up studies, such as marrow or tumor biopsies, x-rays, photographs, etc., are of the greatest clinical importance in evaluating the therapeutic response and should be resorted to as frequently as possible.

Toxicity. Early workers conclusively showed that the nitrogen mustards were not tumor-selective in their action but damaged other cell types as well. To date no compound has been found with highly specific affinity for neoplastic tissue alone. Due to the lack of selectivity of action with currently used drugs damage to other tissues is reflected in the form of several types of toxic reactions which may be conveniently grouped into immediate and late effects:

Immediate Toxic Effects: (1) Pain at the injection site has been most frequently seen when active nitrogen mustard has come into contact with subcutaneous tissues due to faulty venipuncture technic. Areas so contaminated may undergo necrosis and ulceration but usually progress only to moderate inflammation and subsequent healing with induration and pigmentation.[258] (2) Phlebothrombosis at injection sites was observed more frequently in earlier clinical trials with HN_3. Present use of HN_2 administered into the rubber tubing of a rapidly flowing intravenous infusion has reduced this complication to a rarity. (3) Nausea and vomiting are seen in a high percentage of patients within one to eight hours after treatment, persisting as long as forty-eight hours thereafter in some patients. The severity and duration of such symptoms appears to be a function of individual susceptibility, age of the patient (less frequent in children) and adequacy of sedation rather than the size of the dose administered. Administering the drug several hours after the last meal of the day to a patient who is under proper sedation, appears to be of real benefit in decreasing or obviating the emetic effects of these compounds.[255] Accompanying these gastro-

intestinal disturbances, transient anorexia, weakness, headache and weight loss of several pounds are the rule for the next twenty-four to forty-eight hours.

Delayed Toxic Effects: Available data indicate that delayed toxic effects are limited to the hemopoietic system at therapeutic dosage levels and constitute the most potentially dangerous toxic manifestations of nitrogen mustard therapy. Cytotoxic action on bone marrow and lymphatic tissue may progress to complete aplasia of the former and widespread fragmentation of the latter. Careful clinical studies of these phenomena by several groups[258–260] will be briefly summarized.

Peripheral Blood—The initial change noted is a lymphocytopenia appearing within twenty-four hours after initiation of therapy and progressively increasing over the ensuing six to eight days, with a return to normal levels within two weeks. Monocyte levels parallel the changes seen in the lymphocyte series. During the maximum depression period degenerating cells of these two series have been seen in Hodgkin's disease patients and attention is called to their resemblance to blast forms in stained smears.[260] Along with these changes the total leukocyte count declines progressively for fifteen to twenty-one days to variable levels, this fall being largely due to neutropenia. Degenerative morphologic changes in the granulocytes and the appearance of myelocytes in the blood smear may be seen during development of this leukopenia. Recovery may be heralded by a monocytosis with a "shift to the left" in the granulocytes and is usually complete within the ensuing two weeks. Although profound leukopenia and granulocytopenia have been induced in some patients by nitrogen mustard compounds, the "agranulocytic syndrome" with indolent and serious infections has not been reported. This is, no doubt, attributable in part to the prophylactic use of penicillin, blood transfusions and other supportive measures; however, equally important is the fact that bone marrow function returns promptly. Pentnucleotide, ferrous adenylate, leukocytic extracts, folic acid and whole blood have not hastened marrow recovery.[259]

Variable degrees of thrombocytopenia are seen during the third week after a course of therapy, occasionally progressing to low levels with purpura, impaired clot retraction and prolonged bleeding times. A return of platelets to normal levels within the ensuing seven to ten days is the rule. Recently a coagulation defect characterized by prolonged clotting time has been described in some patients and in experimental animals two weeks following nitrogen mustard administration.[282] The evidence indicates that this may be due to hyperheparinemia inasmuch as it can be quickly corrected by parenteral injection of toluidine blue or protamine.

A slight fall in hemoglobin, rarely exceeding 1 Gm. per cent, and a decrease in red blood cell count with concomitant depression of reticulocytes may be seen during the first two weeks after a course of treatment, and occasionally a rise in reticulocytes can be detected two to three weeks post-therapy. These findings are of little clinical consequence, however, since an improvement in pre-existent anemia is common in patients responding favorably to the nitrogen mustards.

Bone Marrow—Serial studies of bone marrow have demonstrated cytotoxic effects of the mustard compounds on both mature and immature elements, with progression to almost total aplasia at high dosage levels. The extreme importance of this observation must be borne in mind when successive courses of therapy are initiated. No cumulative effects on the marrow have been reported in those patients in whom sufficient time for complete marrow regeneration has elapsed between courses of nitrogen mustard. Spurr believes that on the basis of his observations recovery cannot be considered complete for six weeks.[259,260]

Other toxic effects—Studies of hepatic and renal function have disclosed no evidence of toxic effects on these organs following HN therapy.

Clinical Results. An analysis of early results cannot accurately appraise the overall clinical course or survival rate in patients thus far treated with nitrogen mustard compounds. However, it is important to examine the reported series to determine duration of remissions following single courses of therapy and to compare the use of nitrogen mustard with radiotherapy in certain cases. In Table IV an attempt has been made to indicate those conditions in which therapeutic responses have been good and those in which results have been poor or, at best, only fair. Some treatment failures have been seen in every group of patients studied, and in many instances remissions have been brief or inferior to those obtained by conventional therapy technics.

TABLE IV
REPORTED RESPONSES TO HN THERAPY*

Favorable Response	Equivocal Response	No Response
Hodgkin's disease, 253, 255, 256, 258–262, 264, 265, 270–281	Schminke tumor (lympho-epithelioma), 268	Acute leukemia, 253, 255, 258–263, 271, 275–277, 279, 281
Lymphoblastoma, 265, 272	Boeck's sarcoid, 267	Aleukemic leukemia, 258
Giant follicular lymphoma, 253, 258, 261, 262, 274, 276, 280	Disseminated lupus erythematosus, 257	Central nervous system tumors, 271
Lymphosarcoma, 253, 255–259, 261–263, 270, 271, 275, 277, 278, 281	Neuroblastoma, 259, 261, 262, 268, 271	Carcinoma of lung (squamous cell), 255, 271
Chronic lymphatic leukemia, 253, 255, 258–262, 264, 270, 271, 276–278	Ewing's tumor, 272, 284	Carcinoma of genito-urinary, gastro-intestinal tracts, oral cavity, 271
Chronic myelogenous leukemia, 253, 255, 258–262, 264, 270, 271, 281		Carcinoma of breast, 253, 261, 262
Polycythemia vera, 259, 261, 271, 276, 283		Melanosarcoma, 253, 261, 262, 265, 271
Rhabdomyosarcoma, 268		Fibrosarcoma, 255
Mycosis fungoides, 256–258, 265, 266, 269, 270, 272, 276, 285		Kaposi sarcoma, 255, 257
Cancer of lung (anaplastic), 258, 261, 262, 271, 276, 283		Osteogenic sarcoma, 284
		Reticulum cell sarcoma, 277, 280, 281

* Numbers refer to references.

Evaluation of HN Responses. Hodgkin's Disease: The usual immediate response of this group of patients to HN therapy is characterized by a strikingly rapid return of temperature to normal, a sense of well being and an increase in appetite. Within one to two weeks lymphadenopathy, splenomegaly, hepatomegaly and jaundice, as well as bone pain, pruritus, dyspnea, cough, dysphagia and neurologic symptoms of short duration may show striking regression or disappearance, with beginning weight gain and improvement in anemia.

The duration of remission of symptoms is extremely variable in these patients. Rhoads[271] states that a preliminary analysis of a large series would indicate 70 per cent of persons with Hodgkin's disease will show objective response to the drug but that the average remission so induced will persist only one month. It seems clear, however, that many factors other than duration of remission should be considered since they affect the choice of therapeutic measures. Instances of marked improvement have been noted in patients previously refractory to radiotherapy and it has been suggested[253] that x-ray responsiveness may return after a course of nitrogen mustard therapy in some of these patients. In patients with obstructive phenomena due to tumor masses a more rapid therapeutic response can be expected following nitrogen mustard than radiotherapy, and in instances of widely disseminated disease with systemic symptoms the reaction to HN is usually superior to that of roentgen irradiation.[263] There is

general agreement that well localized disease without systemic effects is best treated by conventional radiotherapy technics.

Lymphoma Group (lymphoma, lymphoblastoma, leukosarcoma, lymphosarcoma, reticulum cell sarcoma): While responses in this group of patients have been more variable than in those with Hodgkin's disease, immediate reactions to mustard therapy have often been dramatic enough in well advanced or even moribund cases to demonstrate conclusively a cytotoxic effect in these disease processes. Instances of rapid disappearance of peripheral, intrathoracic, abdominal and retroperitoneal tumor masses, with complete relief of systemic and local symptoms, have been noted by many observers. In early or benign cases of giant follicular lymphoma nitrogen mustard may be expected to produce responses equal to those obtained with x-ray.[263] In rapidly growing, invasive or x-ray resistant lympho- or leukosarcoma HN therapy gives rather disappointing results as a rule.[255,263,276] It seems obvious from patients so far observed that nitrogen mustard is not superior to irradiation in this lymphoma group but may be of real value for short periods of time in widespread disease processes as palliative therapy.

Leukemias: No convincing evidence can be marshalled to support the use of currently employed nitrogen mustard compounds in acute leukemias regardless of cell type. In chronic myelogenous (myeloid) leukemia a favorable response is evidenced by a fall in leukocytes to normal levels, a decrease in spleen size, a rise in red cell count and hemoglobin and disappearance of fever if present. Some patients have been maintained in good health by repeated two to three-day courses of mustard therapy at two to six-week intervals;[255] however, results of a larger series[271] disclose that remissions as a rule are shorter than (although qualitatively similar to) those obtained with x-radiation in early or moderately advanced cases. Wintrobe believes that patients with chronic lymphatic leukemia in whom an abnormal myelogram is the only significant finding respond well to HN therapy as evidenced by a return of blood cell values to normal ranges; while those with marked anemia, adenopathy, splenomegaly and thrombopenia show little if any therapeutic benefit from such drugs.[255] Rhoads points out[271] in a larger group of cases that bone marrow hypoplasia following mustard may be severe in chronic lymphatic leukemia patients and, for this reason and the fact that the remissions observed have been limited and transient in this series, does not recommend nitrogen mustard chemotherapy in this disease.

Miscellaneous: In a limited number of patients with polycythemia vera relief of dizziness, headache, listlessness and lassitude and return of blood values to normal levels have been observed with alkylamine therapy. Remissions have not been superior to those obtained with radioactive phosphorus but it can be concluded that the nitrogen mustards furnish the clinician with an additional therapeutic tool in this disease.

Regarding mycosis fungoides, no convincing demonstration of nitrogen mustard's superiority over x-ray therapy has been reported. Many temporary although brief responses have been observed in patients refractory to radiation. Post-treatment biopsies have shown marked clearing of reticulum cell infiltration in isolated cases[266] associated with clinically observable healing of skin lesions and disappearance of pruritus during the remission phase.

Some favorable therapeutic responses have been observed in Boeck's sarcoid, Ewing's tumor of bone, multiple myeloma, disseminated lupus erythematosus, anaplastic carcinoma of the lung, lymphoepithelioma (Schmincke tumor), rhabdomyosarcoma and neuroblastoma (including sympathicoblastoma), the exact significance of which must remain unsettled until further clinical trials can be undertaken.

Comment. There seems to be clear indication for use of nitrogen mustard compounds, preferably the methyl bis derivative at the present writing, in the treatment of Hodgkin's disease, the lymphomas, some

cases of chronic leukemia, inoperable carcinoma of the lung of anaplastic histology and mycosis fungoides. To say that these are the drugs or treatments of choice is not justified according to available evidence. Such factors as degree of dissemination, with or without obstructive phenomena from tumor masses, refractiveness to other forms of therapy and level of peripheral blood cell values will, in the final appraisal of the patient, dictate the course of action to be taken.

In acute leukemias, squamous cell carcinoma of the lung, carcinoma of the oral cavity, gastrointestinal and genito-urinary tracts, central nervous system tumors and most types of sarcomas not included in the preceding categories little or no justification for mustard chemotherapy exists. In the case of acute leukemias, regardless of cell type, use of these drugs may accelerate the progress of the disease to an earlier fatal termination on the basis of some reports.[253]

An intermediate group of conditions exists, including multiple myeloma, neuroblastomas, Ewing's tumor of bone, lymphoepithelioma (Schmincke tumor) and Boeck's sarcoid, in which further clinical trial is needed to appraise the merits of alkylamine therapy. In this connection it can be said that a therapeutic trial may be the only means of determining the efficacy of these compounds in a given patient, and certainly there should be no hesitation in offering this group of patients the chance of effective palliative measures when usual ones have failed.

Future developments in the field of tumor chemotherapy will undoubtedly change this picture since an enormous number of related alkylamines remain untried clinically or in the laboratory. The ideal drug would exhibit no toxic side actions and would possess cytotoxic effects confined to pathologic tissue. None such has yet been found.

CONCLUSION

The foregoing presentation did not include all of the chemical agents currently employed in the treatment of malignant disease. Karnofsky's recent review includes a number of agents not discussed herein.[286] Notably omitted from the discussion was the radioactive isotope group of drugs. These agents have contributed and undoubtedly will increasingly contribute significantly to the therapy of cancer. However, since they constitute a specialized form of radiotherapy, they were considered to be outside the scope of this paper.

From the survey which has been made it is possible to draw certain specific conclusions. It is believed that the available evidence warrants the following applications of cancer chemotherapy in medical practice: (1) androgen control therapy of prostatic malignancy when the neoplasm has extended beyond the confines of the gland; (2) urethane in the therapy of chronic myeloid and lymphatic leukemia when radiotherapy is not available or is contraindicated; (3) nitrogen mustard therapy of disseminated malignant lymphomas either as an adjunct to radiotherapy or as an alternate form of therapy.

It is further believed that the following agents merit trial after conventional therapy has proved without avail: (1) androgenic hormone in carcinoma of the breast with skeletal metastases and (2) stilbamidine in multiple myeloma in the presence of intractable pain.

Finally, it is our belief that (1) there is no objective indication that antireticular cytotoxic serum and pteroyltriglutamic acid (teropterin) have any effect on malignant disease and they should therefore not be employed; (2) use of estrogen in the therapy of carcinoma of the breast with soft tissue metastases in postmenopausal women has not been sufficiently explored to recommend its general employment; (3) products of micro-organisms have real potentialities as carcinolytic agents but their value in the therapy of human neoplastic disease has not been demonstrated up to the present.

It is apparent that there are severe limitations to the chemotherapy of cancer at this time. None of the agents discussed has cured cancer and in most instances the

beneficial effects have been relatively transient. Frequently, these facts are interpreted as conclusive evidence that the cure of disseminated malignant disease presents a hopeless problem. This would appear to be a superficial evaluation for the fact remains that several of the drugs which have been discussed destroy malignant cells without destroying the host. To reconcile this undeniable evidence with the observation that only remissions and not cures are produced by chemotherapy in malignant disease is not easy. One explanation which is compatible with the facts is that among the cells of a susceptible tumor there is variation in resistance to the cytotoxic agent which may be a primary or an acquired characteristic. This would be analogous to the situation encountered in infection when micro-organisms become resistant to chemotherapeutic drugs. The problem of drug-resistant micro-organisms has been largely overcome by utilizing several effective antimicrobial agents either simultaneously or in alternate therapeutic courses. When it is recalled that androgen control therapy of prostatic malignancy, urethane and nitrogen mustards have all been developed within the past seven years, it does not seem unreasonable to anticipate additional potent carcinolytic agents in the not too distant future. With an enlarged therapeutic armamentarium, the possibilities for a combined attack on malignant disease offer an attractive and hopeful prospect.

REFERENCES

1. Ackerman, L. V. and del Regato, J. A. Cancer. St. Louis, 1947. C. V. Mosby Co.
2. Simpson, W. M. Progress in cancer research. *Am. J. Clin. Path.*, 17: 513, 1947.
3. Busch, W. vi. Verhandlungen ärztlicher Gesellschaften. *Berl. klin. Wchnschr.*, 3: 245, 1866.
4. Fehleisen. Ueber die Züchtung der Erysipelkokken auf künstlichen Nährboden und ihre Ueberträgbarkeit auf den Menschen. *Deutsche med. Wchnschr.*, 8: 553, 1882.
5. Spronck, C. H. H. Tumeurs malignes et maladies infectieuses. *Ann. Inst. Pasteur*, 6: 683, 1892.
6. Beebe, S. P. and Tracy, M. The treatment of experimental tumors with bacterial toxins. *J. A. M. A.*, 49: 1493, 1907.
7. Gratia, A. and Linz, R. Le phénomène de Shwartzman dans le sarcome du cobaye. *Compt. rend. Soc. de biol.*, 108: 427, 1931.
8. Shwartzman, G. and Michailovsky, N. Phenomenon of local skin reactivity to bacterial filtrates in treatment of mouse sarcoma 180. *Proc. Soc. Exper. Biol. & Med.*, 29: 737, 1932.
9. Shear, M. J. and Andervont, H. B. Annual report of the Surgeon General of the Public Health Service of the U. S. Washington, D. C., 1932.
10. Shear, M. J. Studies on the chemical treatment of tumors. ii. The effect of disturbances in fluid exchange on transplanted mouse tumors. *Am. J. Cancer*, 25: 66, 1935.
11. Andervont, H. B. The reaction of mice and of various mouse tumors to the injection of bacterial products. *Am. J. Cancer*, 27: 77, 1936.
12. Shear, M. J. and Turner, F. C. Studies on the chemical treatment of tumors. v. Separation of the hemorrhage-producing fraction from Bacillus prodigiosus filtrates. *J. Biol. Chem.*, 133: 87, 1940.
13. Idem. Studies on the chemical treatment of tumors. v. Isolation of the hemorrhage-producing fraction from Serratia marcescens (Bacillus prodigiosus) culture filtrate. *J. Nat. Cancer Inst.*, 4: 81, 1943.
14. Shear, M. J., Perrault, A. and Adams, J. R., Jr. Chemical treatment of tumors. vi. Method employed in determining the potency of hemorrhage-producing bacterial preparations. *J. Nat. Cancer Inst.*, 4: 99, 1943.
15. Hartwell, J. L., Shear, M. J. and Adams, J. R., Jr. vii. Nature of the hemorrhage-producing fraction from Serratia marcescens (Bacillus prodigiosus) culture filtrate. *J. Nat. Cancer Inst.*, 4: 107, 1943.
16. Shear, M. J. Chemical treatment of tumors. ix. Reactions of mice with primary subcutaneous tumors to injection of hemorrhage-producing bacterial polysaccharide. *J. Nat. Cancer Inst.*, 4: 461, 1944.
17. Daels, F. Beitrag zum Studium des Antagonismus zwischen den Karzinom-, Spirillen- und Trypanosomeninfektionen. *Arch. f. Hyg.*, 72: 257, 1910.
18. Comsia, O. L'antagonisme entre la spirochetose recurrente et le cancer expérimental chez les souris. *Compt. rend. Soc. de biol.*, 99: 900, 1928.
19. Roskin, G. and Exampliarskaia, E. Protozoeninfektion und experimenteller Krebs. *Ztschr. f. Krebsforsch.*, 34: 628. 1931.
20. Roskin, G. Toxin therapy of experimental cancer; the influence of protozoan infections upon transplanted cancer. *Cancer Research*, 6: 363, 1946.
21. Roskin, G. Toxin therapy of experimental cancer. *Am. Rev. Soviet Med.*, 4: 111, 1946.
22. Malisoff, W. M. The action of the endotoxin of Trypanosoma cruzi (KR) on malignant mouse tumors. *Science*, 106: 591, 1947.
23. Hauschka, T. S. Sex of host as a factor in Chagas' disease. *J. Parasitol.*, 33: 399, 1947.
24. Hauschka, T. S. Trypanosoma cruzi "endotoxin" in the treatment of mouse tumors. Abstracts of 4th Internat. Cancer Research Congress. P. 89. September, 1947.
25. Hauschka, T., Saxe, L. H., Jr. and Blair, M. Trypanosoma cruzi in the treatment of mouse tumors. *J. Nat. Cancer Inst.*, 7: 189, 1947.

26. Hauschka, T. S. and Goodwin, M. B. Trypanosoma cruzi endotoxin (KR) in the treatment of malignant mouse tumors. *Science*, 107: 600, 1948.
27. Cohen, A. L., Borsook, H. and Dubnoff, J. W. The effect of a sparosarcina ureae preparation on tumor cells *in vitro*. *Proc. Soc. Exper. Biol. & Med.*, 66: 440, 1947.
28. Arthus, M. Injections répétées de serum de cheval chez le lapin. *Compt. rend. Soc. de biol.*, 55: 817, 1903.
29. Wilson, G. S. and Miles, A. A. Topley and Wilson's Principles of Bacteriology and Immunity. Baltimore, 1946. Williams & Wilkins Co.
30. Shwartzman, G. A new phenomenon of local skin reactivity to B. typhosus culture filtrate. *Proc. Soc. Exper. Biol. & Med.*, 25: 560, 1927–1928.
31. Hanger, F. M., Jr. Effect of intravenous bacterial filtrates on skin tests and local infections. *Ibid.*, 25: 775, 1927–1928.
32. Shwartzman, G. Phenomenon of Local Tissue Reactivity. New York, 1937. Paul B. Hoeber, Inc.
33. Duran-Reynals, F. Reaction of transplantable and spontaneous tumors to blood-carried bacterial toxins in animals unsusceptible to the Shwartzman phenomenon. *Proc. Soc. Exper. Biol. & Med.*, 31: 341, 1933.
34. Apitz, K. Über Blutungsreaktionen im Impfcarcinom der Maus. *Ztschr. f. Krebsforsch.*, 40: 50, 1933.
35. Shear, M. J. Studies on the chemical treatment of tumors. ii. The effect of disturbances in fluid exchange on transplanted mouse tumors. *Am. J. Cancer*, 25: 66, 1935.
36. Duran-Reynals, F. Reaction of spontaneous mouse carcinoma to blood-carried bacterial toxins. *Proc. Soc. Exper. Biol. & Med.*, 32: 1517, 1935.
37. Coley, W. B. Contribution to the knowledge of sarcoma. *Ann. Surg.*, 14: 199, 1891.
38. Idem. The diagnosis and treatment of bone sarcoma. *Glasgow M. J.*, 126: 49, 1936.
39. Nauts, H. C., Swift, W. E. and Coley, B. L. The treatment of malignant tumors by bacterial toxins as developed by the late William B. Coley, m.d., reviewed in the light of modern research. *Cancer Research*, 6: 205, 1946.
40. Tracy, M. A study of the toxins of Bacillus prodigiosus. *J. M. Research*, 16: 307, 1907–1908.
41. Fowler, G. R. The use of animal toxins in the treatment of inoperable malignant tumors. *Am. J. M. Sc.*, 116: 161, 1898.
42. Brues, A. M. and Shear, M. J. Chemical treatment of tumors. x. Reactions of four patients with advanced malignant tumors to injection of a polysaccharide from Serratia marcescens culture filtrate. *J. Nat. Cancer Inst.*, 5: 195, 1944.
43. Holloman, A. L. Reactions of patients and of tumors to injection of S. marcescens polysaccharide in eight cases of malignant disease. P. 273. Approaches to Tumor Chemotherapy. American Association for the Advancement of Science, 1947.
44. Oakey, R. Reactions of patients to injection of S. marcescens polysaccharide in nine further cases of malignant disease. P. 277. Approaches to Tumor Chemotherapy. American Association for the Advancement of Science, 1947.
45. Klyueva, N. G. Paths of cancer biotherapy. *Am. Rev. Soviet Med.*, 4: 408, 1947.
46. Stern, K. and Willheim, R. The Biochemistry of Malignant Tumors. Chapt. 8. Reference Press, 1943.
47. Babes, A. La rate chez les lapins avec cancer du goudron. *Bull. Assoc. franc. p. l'etude du cancer*, 19: 232, 1930.
48. Twort, J. M. and Lasnitzki, M. Studies on the pituitary weight of rats inoculated with a transmissible tumor. *Endocrinology*, 23: 87, 1938.
49. Brown, W. H. and Pearce, L. The reaction of the endocrine system of the rabbit to tumor inoculation and the relation of this reaction to malignancy. *Proc. Soc. Exper. Biol. & Med.*, 20: 472, 1923.
50. Sure, B., Theis, R. M. and Harrelson, R. T. Influence of Walker carcinosarcoma on concentration of ascorbic acid in various endocrines and organs. *Am. J. Cancer*, 36: 252, 1939.
51. Roffo, A. H. Eine biologische Reaktion der Milz, hervorgerufen durch bluttumorbehafteten Ratten. *Ztschr. f. Krebsforsch.*, 30: 180, 1929.
52. Beard, H. H., Halperin, B. and Libert, S. A. Effect of intraperitoneal injection of malignant urine extracts in normal and hypophysectomized rats. *Science*, 105: 475, 1947.
53. Flantchik, L. I. Morphological and biological characteristics of cancer metastasis in the spleen. *Am. J. Cancer*, 31: 152, 1937.
54. Andervont, H. B. The influence of trypan blue upon the resistance of mice to transplantable and induced tumors. *Pub. Health Rep.*, 51: 591, 1936.
55. Khaletzaya, F. M. The influence of splenectomy upon the development of tumors induced by chemical agents. *Am. J. Cancer*, 40: 262, 1940.
56. Latta, J. S. and Johnson, H. N. Studies of lymphatic tissue grown *in vitro* with splenic extract as culture medium. *Arch. f. exper. Zellforsch.*, 16: 221, 1934.
57. Jones, L. O. *In vitro* studies on the effect of spleen, striated muscle, and kidney upon the growth of sarcoma 180 and mammary carcinoma in mice. *Cancer Research*. (In press.)
58. Bogolomets, A. A. Anti-reticular cytotoxic serum as a means of pathogenetic therapy. *Am. Rev. Soviet Med.*, 1: 101, 1943.
59. Straus, R. Studies on anti-reticular cytotoxic serum. i. Introduction and review of the literature. *J. Immunol.*, 54: 151, 1946.
60. Fedyushin, M. P. The experimental application of anti-reticular cytotoxic serum in cancer cases. Quoted by Straus, R.[59]
61. Straus, R., Runjavac, M., Zaitlin, R., Duboff, G. and Swerdlow, H. Studies on anti-reticular cytotoxic serum. ii. Preparation and titration of the serum and study of its serological properties. *J. Immunol.*, 54: 155, 1946.
62. Straus, R., Horwitz, M., Levinthal, H., Cohen, A. L. and Runjavac, M. Studies on anti-reticular cytotoxic serum. iii. Effect of ACS on the healing of experimentally produced fractures in rabbits. *J. Immunol.*, 54: 163, 1946.
63. Marchuk, P. D. A method of preparing and pre-

serving anti-reticular cytotoxic serum. *Am. Rev. Soviet Med.*, 1: 113, 1943–1944.

64. Davis, W. D., Jr. Clinical observations in patients treated with anti-reticular cytotoxic serum. Preliminary report. Meet., Am. Fed. Clin. Research. April 8, 1947. *Am. J. Med.*, 3: 123, 1947.
65. Friedman, R. and Stritzler C. Mycosis fungoides resisting treatment with both nitrogen mustard and anti-reticular cytotoxic serum. *J. Invest. Dermat.* 10: 227, 1948.
66. Skapier, J. Therapeutic use of anti-reticular cytotoxic serum (ACS) in Hodgkin's disease. *Cancer Research*, 7: 369, 1947.
67. Rogoff, B., Freyberg, R. H., Powell, H. M. and Rice, R. M. Experiences with antireticular cytotoxic serum (ACS) in arthritis. *Am. J. M. Sc.*, 214: 395, 1947.
68. Watson, G. F., Diller, I. C. and Ludwick, N. V. Spleen extract and tumor growth. *Science*, 106: 348, 1947.
69. Lewisohn, R. Effect of subcutaneous injections of concentrated spleen extract on mouse sarcoma 180. *Surg. Gynec., & Obst.*, 66: 563, 1938.
70. Lewisohn, R. Chemotherapeutic regressions of transplanted and spontaneous cancers in mice. I. Review of the work of the laboratory 1937–1945. Approaches to Tumor Chemotherapy. P. 139. American Association for the Advancement of Science, 1947.
71. Leuchtenberger, C., Lewisohn, R., Lazlo, D. and Leuchtenberger, R. "Folic acid" a tumor growth inhibitor. *Proc. Soc. Exper. Biol. & Med.*, 55: 204, 1944.
72. Leuchtenberger, R., Leuchtenberger, C., Lazlo, D. and Lewisohn R. The influence of "folic acid" on spontaneous breast cancers in mice. *Science*, 101: 46, 1945.
73. Leuchtenberger, C. Results of treatment of spontaneous tumors with "folic acid" and allied substances. Approaches to Tumor Chemotherapy. P. 157. American Association for the Advancement of Science, 1947.
74. Sugiura, K. Effect of intravenous injection of yeast and barley extracts and L. casei factor upon spontaneous mammary adenocarcinoma in mice. Approaches to Tumor Chemotherapy. P. 208. American Association for the Advancement of Science, 1947.
75. Burk, D. A discussion of C. Leuchtenberger's paper.[73]
76. Morris, H. P. A discussion of Leuchtenberger's paper.[73]
77. Farber, S., Cutler, E. C., Hawkins, J. W., Harrison, J. H., Pierce, E. C. and Lenz, G. G. The Action of pteroylglutamic conjugates on man. *Science*, 106: 619, 1947.
78. Klainer, M. J. A case report of metastatic carcinoma treated with teropterin. *Tr. New York Acad. Sc.*, 10: 71, 1948.
79. Lehv, S. P., Wright, L. T., Weintraub, S. and Arons, I. Use of teropterin in neoplastic disease: a preliminary clinical report. *Tr. New York Acad. Sc.*, 10: 75, 1948.
80. Meyer, L. M. Use of folic acid derivatives in the treatment of human leukemia. *Tr. New York Acad. Sc.*, 10: 99, 1948.
81. Welch, A. D. The present status of pteroylglutamic acid and of other hematopoietic agents. *Federation Proc.*, 6: 471, 1947.
82. Woll, E. The Rous chicken sarcoma in birds treated with folic acid and its derivatives: a pathological study. *Tr. New York Acad. Sc.*, 10: 83, 1948.
83. Little, P. A., Sampath, A., Paganelli, V., Locke, E. and SubbaRow, Y. The effect of folic acid and its antagonists on Rous chicken sarcoma. *Tr. New York Acad. Sc.*, 10: 91, 1948.
84. Council on Pharmacy and Chemistry. "Teropterin" and "diopterin" in the treatment of cancer. *J. A. M. A.*, 137: 699, 1948.
85. Wooley, D. W. Recent advances in study of biological competition between structurally related compounds. *Physiol. Rev.*, 27: 308, 1947.
86. Hutchings, B. L. Pteroylaspartic acid an antagonist for pteroylglutamic acid. *J. Biol. Chem.*, 170: 323, 1947.
87. Seeger, D. R., Smith, J. M., Jr. and Hultquist, M. E. Antagonist for pteroylglutamic acid. *J. Am. Chem. Soc.*, 69: 2567, 1947.
88. Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F. and Wolff, J. A. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroylglutamic acid (aminopterin). *New England J. Med.*, 238: 787, 1948.
89. Farber, S. Papers presented at the International Congress of Hematology, Buffalo, August, 1948 and the American Cancer Society meetings, New York, November, 1948.
90. Dameshek, Wm. The use of folic acid antagonists in acute leukemia. *Blood*, 3: 1057, 1948.
91. Strong, R. P. Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases. Philadelphia, 1944. The Blakiston Co.
92. Yorke, W. Recent work on chemotherapy of protozoal infections. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 33: 463, 1940.
93. Adams, A. R. D. and Yorke, W. Studies in chemotherapy. XXIII. A case of Indian kala-azar treated with 4:4′-diamidino stilbene. *Ann. Trop. Med.*, 33: 323, 1939.
94. Snapper, I. On the influence of stilbamidine upon multiple myeloma. *J. Mt. Sinai Hosp.*, 13: 119, 1946.
95. Snapper, I. Stilbamidine and pentamidine in multiple myeloma. *J. A. M. A.*, 133: 157, 1947.
96. Snapper, I. and Schneid, B. On the influence of stilbamidine upon myeloma cells. *Blood*, 1: 534, 1946.
97. Snapper, I., Mirsky, A. E., Ris, H., Schneid, B. and Rosenthal, M. Development of inclusion bodies containing ribose nucleic acid in myeloma cells after injections of stilbamidine. Determination of stilbamidine in myeloma tissue. *Blood*, 2: 311, 1947.
98. Kopac, M. J. Cellular mechanisms in chemotherapy. *Tr. New York Acad. Sci.*, 8: 5, 1945.
99. Eisen, M. J. Transplantable carcinoma of the rat breast. *Am. J. Cancer*, 39: 36, 1940.
100. Murphy, J. B. and Sturm, E. The transmission of

an induced lymphatic leukemia and lymphosarcoma in the rat. *Cancer Research*, 1: 379, 1941.
101. Snapper, I. Treatment of multiple myeloma with "stilbamidine." Clinical results and morphologic changes. *J. A. M. A.*, 137: 513, 1948.
102. Fulton, J. D. and Yorke, W. xxxi. The increased toxicity of old solutions of stilbamidine. *Ann. Trop. Med.*, 36: 134, 1942.
103. Arai, H. and Snapper, I. The influence of stilbamidine upon kidney function, liver function and peripheral blood in multiple myeloma. Neurologic sequelae of stilbamidine therapy. *New York State J. Med.*, 47: 1867, 1947.
104. Napier, L. E. and Sen Gupta, P. C. A peculiar neurological sequel to administration of 4:4′-diamidino-diphenyl-ethylene. *Indian M. Gaz.*, 77: 71, 1942.
105. Sen Gupta, P. C. Observations of the neuropathic sequel of diamidinostilbene therapy in kala-azar. *Ibid.*, 78: 537, 1943.
106. Kirk, R. and Henry, A. J. Observations on the toxicity of stilbamidine. *Ann. Trop. Med.*, 38: 99, 1944.
107. Oastler, E. G. and Fidler, H. K. Cerebral lesions produced in healthy dogs by the intravenous injection of 4:4′-diamidino stilbene. *Tr. Roy. Soc. Trop. Med.*, 39: 533, 1946.
108. Rubinstein, M. A. Chemotherapy of multiple myeloma: the use of antimony. *Blood*, 2: 555, 1947.
109. Ling, S. M. Distribution of protein fractions in the serum of kala-azar patients. *Proc. Soc. Exper. Biol. & Med.*, 27: 247, 1930.
110. Gutman, A. B., Moore, D. H., Gutman, E. B., McClellan, V. and Kabat, E. A. Fractionation of serum proteins in hyperproteinemia with special reference to multiple myeloma. *J. Clin. Investigation*, 20: 765, 1941.
111. Moore, D. H., Kabat, E. A. and Gutman, A. B. Bence-Jones proteinemia in multiple myeloma. *J. Clin. Investigation*, 22: 67, 1943.
112. Haddow, A. and Sexton, W. A. Influence of carbamic esters (urethanes) on experimental animal tumors. *Nature, London*, 157: 500, 1946.
113. Clark, A. J. Mode of Action of Drugs on Cells. London, 1933.
114. Quastel, J. H. Effects of narcotics and benzedrine on metabolic processes in the central nervous system. *Tr. Faraday Soc.*, 39: 348, 1943.
115. Johnson, F. H., Eyring, H., Steblay, R., Chaplin, H., Huber, C. and Gherardi, G. The nature and control of reactions in bioluminescence. *J. Gen. Physiol.*, 28: 463, 1945.
116. Plentl, A. A. and Schoenheimer, R. Studies in the metabolism of purines and pyrimidines by means of isotopic nitrogen. *J. Biol. Chem.*, 153: 203, 1944.
117. Paterson, E., Haddow, A., ApThomas, M. I. R., and Watkinson, J. M. Leukemia treated with urethane compared with deep x-ray therapy. *Lancet*, 1: 677, 1946.
118. Murphy, J. B. and Sturm, E. The effect of urethane on lymphatic leukemia in rats. *Science*, 104: 386, 427, 1946.
119. Engstrom, R. M., Kirschbaum, A. and Mixer, H. W. Effect of urethane on mouse myelogenous leukemia. *Science*, 105: 255, 1947.
120. Weir, D. R. and Heinle, R. W. Effect of urethane on transplanted leukemia of Ak mice. *Proc. Soc. Exper. Biol. & Med.*, 66: 268, 1947.
121. Law, L. W. Effect of urethane on a transplantable acute lymphoid leukemia. *Proc. Soc. Exper. Biol. & Med.*, 66: 158, 1947.
122. Skipper, H. E., Riser, W. H., Jr., Stelzenmuller, A. and Holt, H. Carbamates in the chemotherapy of leukemia. *Blood*, 3: 774, 1948.
123. Watkins, C. H. Evaluation of therapeutic agents in recent use in the control of experimental and human leukemia. *Proc. Inst. Med. Chicago*, 16: 386, 1947.
124. Creskoff, A. J., Fitz-Hugh, T. and Frost, J. W. Urethane therapy in leukemia. *Blood*, 3: 896, 1948.
125. Hirschboeck, J. S., Lindert, M. C. F., Chase, F. and Calvey, T. L. Effects of urethane in the treatment of leukemia and metastatic malignant tumors. *J. A. M. A.*, 136: 90, 1948.
126. Watkins, C. H., Cooper, T. and Griffin, H. Z. The use of urethane (ethylcarbamate) in the treatment of leukemia. *Blood*, 3: 892, 1948.
127. McAlister, J. P. Leukemia treated with urethane. *Arkansas M. Soc. J.*, 44: 139, 1947.
128. Berman, L. and Axelrod, A. R. Effect of urethane on malignant diseases. Clinical, hematologic and histologic observations on patients with carcinoma, leukemia and related diseases. *Am. J. Clin. Path.*, 18: 104, 1948.
129. Goodman, M. J. and Lewis, H. P. Urethane in leukemia. *J. A. M. A.*, 132: 1105, 1946.
130. Huggins, C., Yu, S. T. and Jones, R., Jr. Inhibitory effects of ethyl carbamate on prostatic cancer. *Science*, 106: 147, 1947.
131. Webster, J. J. Urethane in leukemia. *J. A. M. A.*, 135: 901, 1947.
132. Civiale, quoted by White, J. W. The present position of the surgery of the hypertrophied prostate. *Ann. Surg.*, 18: 152, 1893.
133. Huggins, C., Masina, M. H., Eichelberger, L. and Wharton, J. D. Quantitative studies of prostatic secretion. i. Characteristics of the normal secretion; the influence of thyroid, suprarenal and testis extirpation and androgen substitution on the prostatic output. *J. Exper. Med.*, 70: 543, 1939.
134. Huggins, C. and Stevens, R. A. The effect of castration on benign hypertrophy of the prostate in man. *J. Urol.*, 43: 705, 1940.
135. Kutscher, W. and Wolbergs, H. Prostataphosphatase. *Ztschr. f. physiol. Chem.*, 236: 237, 1935.
136. Gutman, A. B. and Gutman, E. B. An "acid" phosphatase occurring in the serum of patients with metastasizing carcinoma of the prostate gland. *J. Clin. Investigation*, 17: 473, 1938.
137. Sullivan, T. J., Gutman, E. B. and Gutman, A. B. Theory and application of the serum "acid" phosphatase determination in metastasizing prostatic carcinoma; early effects of castration. *J. Urol.*, 48: 426, 1942.
138. Gomori, G. Distribution of acid phosphatase in the tissues under normal and under pathological conditions. *Arch. Path.*, 32: 189, 1941.

139. Huggins, C. and Hodges, C. V. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Research*, 1: 293, 1941.
140. Huggins, C., Stevens, R. E. and Hodges, C. V. Studies on prostatic cancer. II. The effects of castration on advanced carcinoma of the prostate gland. *Arch. Surg.*, 43: 209, 1941.
141. Gutman, E. B., Sproul, E. E. and Gutman, A. B. Significance of increased phosphatase activity of bone at site of osteoplastic metastases secondary to carcinoma of the prostate gland. *Am. J. Cancer*, 28: 485, 1936.
142. Smith, P. E. and Engle, E. T. Experimental evidence regarding the role of the anterior pituitary in the development and regulation of the genital system. *Am. J. Anat.*, 40: 159, 1927.
143. Moore, C. R. and Price, D. The question of sex hormone antagonism. *Proc. Soc. Exper. Biol. & Med.*, 28: 38, 1930.
144. Huggins, C. and Clark, P. J. Quantitative studies of prostatic secretion. II. The effect of castration and of estrogen injection on the normal and on the hyperplastic prostatic glands of dogs. *J. Exper. Med.*, 72: 747, 1940.
145. Dean, A. L. Carcinoma of the prostate. *Bull. New York Acad. Med.*, 23: 454, 1947.
146. Cori, C. F. Enzymatic reactions in carbohydrate metabolism. Harvey Lectures, 41: 253, 1945–1946.
147. Barron, E. S. G. and Huggins, C. The metabolism of isolated prostatic tissue. *J. Urol.*, 51: 630, 1944.
148. Herbst, W. P. The effects of estradiol dipropionate and diethyl stilbestrol on malignant prostatic tissue. *Tr. Am. A. Genito-Urin. Surgeons*, 34: 195, 1941.
149. Kahle, P. J., Ogden, H. D., Jr. and Getzoff, P. L. The effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate gland. *J. Urol.*, 48: 83, 1942.
150. Heckel, N. J. and Kretschmer, H. L. Carcinoma of the prostate treated with diethylstilbestrol. Histologic alterations. *J. A. M. A.*, 119: 1087, 1942.
151. Chute, R. and Willetts, A. T. The treatment of cancer of the prostate with castration and the administration of estrogen. A preliminary report. *New England J. Med.*, 227: 863, 1942.
152. Dean, A. L., Woodard, H. Q. and Twombly, G. H. The endocrine treatment of cancers of the prostate gland. *Surgery*, 16: 169, 1944.
153. Fergusson, J. D. and Pagel, W. Some observations on carcinoma of the prostate treated with oestrogens as demonstrated by serial biopsies. *Brit. J. Surg.*, 33: 122, 1945.
154. Fergusson, J. D. Carcinoma of the prostate treated with oestrogens. *Lancet*, 251: 551, 1946.
155. McCrea, L. E. Carcinoma of the prostate: a resume of treatment with ethinyl estradiol; preliminary report. *J. Urol.*, 56: 697, 1946.
156. Heckel, N. J. Sex hormone therapy in the treatment of carcinoma of the prostate and benign prostatic hypertrophy. *Clinics*, 5: 860, 1946.
157. Mathé, C. P. and Ardila, C. E. Carcinoma of the prostate. Review of 130 cases treated between 1940 and 1946. *Surg., Gynec. & Obst.*, 84: 276, 1947.
158. Deming, C. L. Present evaluation of the response of prostatic cancer to hormone therapy. *South. M. J.*, 40: 328, 1947.
159. Colston, J. A. C. and Brendler, H. Endocrine therapy in carcinoma of the prostate. Preparation of patients for radical prostatectomy. *J. A. M. A.*, 134: 848, 1947.
160. Buchert, W. I., Culp, D. A. and Jones, G. H. Carcinoma of the prostate gland. An analysis of 135 consecutive cases. *Pennsylvania M. J.*, 51: 165, 1947.
161. Schenken, J. R., Burns, E. L. and Kahle, P. J. The effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate gland. II. Cytologic changes following treatment. *J. Urol.*, 48: 99, 1942.
162. Schwartz, M. The effect of stilbestrol on the testis and breast of patients treated for carcinoma of the prostate gland. *Proc. Am. Federation Clin. Research*, 2: 97, 1945.
163. Moore, G. F., Wattenberg, C. A. and Rose, D. K. Breast changes due to diethylstilbestrol during treatment of cancer of the prostate gland. *J. A. M. A.*, 127: 60, 1945.
164. Abramson, W. and Warshawsky, H. Cancer of the breast in the male secondary to estrogenic administration. Report of a case. *J. Urol.*, 59: 76, 1948.
165. Haagensen, C. D. Personal communication.
166. Thorn, G. W., Nelson, K. R. and Thorn, D. W. A study of the mechanism of edema associated with menstruation. *Endocrinology*, 22: 155, 1938.
167. Bland, E. F. and Nathanson, I. T. Personal communication.
168. Bumpus, H. C., Jr. Carcinoma of the prostate. A clinical study of 1,000 cases. *Surg., Gynec. & Obst.*, 43: 150, 1926.
169. Hovenian, M. S. and Deming, C. L. The heterologous growth of cancer of the human prostate. *Surg., Gynec. & Obst.*, 86: 29, 1948.
170. Lathrop, A. E. C. and Loeb, L. Further investigations on the origin of tumors in mice. III. On the part played by internal secretion in the spontaneous development of tumors. *J. Cancer Research*, 1: 1, 1916.
171. Loeb, L. Further investigations on the origin of tumors in mice. VI. Internal secretion as a factor in the origin of tumors. *J. M. Research*, 40: 477, 1919.
172. Lacassagne, A. Hormonal pathogenesis of adenocarcinoma of the breast. *Am. J. Cancer*, 27: 217, 1936.
173. Lacassagne, A. Tentatives pour modifier par la progestérone ou par la testosterone, l'apparition des adénocarcinomes mammaires provoqués par l'oestroné chez la souris. *Compt. rend. Soc. de biol.*, 126: 385, 1937.
174. Lacassagne, A. Adénocarcinome mammare de la souris et hormones mâles. *Bull. Assoc. franc. p. l'étude du cancer*, 28: 951, 1939.
175. Nathanson, I. T. and Andervont, H. B. Effect of testosterone propionate on development and growth of mammary carcinoma in female mice. *Proc. Soc. Exper. Biol. & Med.*, 40: 421, 1939.

176. Loeser, A. A. Mammary carcinoma. Response to implantation of male hormone and progesterone. *Lancet*, 2: 698, 1941.
177. Ulrich, P. Testosterone (hormone mâle) et son role possible dans le traitement de certains cancers du sein. *Acta, Union internat. contre cancer*, 4: 377, 1939.
178. Fels, E. Treatment of breast cancer with testosterone propionate. A preliminary report. *J. Clin. Endocrinol.*, 4: 121, 1944.
179. Allen, E. Sex and Internal Secretions. Baltimore, 1939. Williams & Wilkins Co.
180. MacBryde, C. M. The production of breast growth in the human female by the local application of estrogenic ointment. *J. A. M. A.*, 112: 1045, 1939.
181. Corner, G. W. The Hormones in Human Reproduction. Princeton, 1942. Princeton University Press.
182. Riddle, O., Bates, R. W. and Dykshorn, S. W. The preparation, identification and assay of prolactin—a hormone of the anterior pituitary. *Am. J. Physiol.*, 105: 191, 1933.
183. Riddle, O. Lactogenic and mammogenic hormones. Glandular Physiology and Therapy. American Medical Association, Chicago, 1942.
184. Gardner, W. U. and White, A. Mammary growth in hypophysectomized male mice receiving estrogen and prolactin. *Proc. Soc. Exper. Biol. & Med.*, 48: 590, 1941.
185. Reichstein, T. and Shopee, C. W. The hormones of the adrenal cortex. Vitamins and Hormones. Vol. I. New York, 1943. Academic Press, Inc.
186. Salmon, U. J. Effect of testosterone propionate upon gonadotrophic hormone excretion and vaginal smears of human female castrate. *Proc. Soc. Exper. Biol. & Med.*, 37: 488, 1937.
187. Long, C. N. H. The conditions associated with the secretion of the adrenal cortex. *Federation Proc.*, 6: 461, 1947.
188. Shorr, E., Papanicolaou, G. N. and Stimmel, B. F. Neutralization of ovarian follicular hormone in women by simultaneous administration of male sex hormone. *Proc. Soc. Exper. Biol. & Med.*, 38: 759, 1938.
189. Robson, J. M. Relative effectiveness of testosterone and of progesterone in the inhibition of oestrus and of the vaginal action of oestrin in mice. *J. Physiol.*, 90: 15P, 1937.
190. Albright, F. Osteoporosis. *Ann. Int. Med.*, 27: 861, 1947.
191. Reifenstein, E. C., Jr. and Albright, F. The metabolic effects of steroid hormones in osteoporosis. *J. Clin. Investigation*, 26: 24, 1947.
192. Kenyon, A. T., Knowlton, K., Sandiford, I., Koch, F. C. and Latwin, G. A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism. *Endocrinology*, 26: 26, 1940.
193. Abels, J. C., Young, N. F. and Taylor, H. C., Jr. Effects of testosterone and of testosterone propionate on protein formation in man. *J. Clin. Endocrinol.*, 4: 198, 1944.
194. Farrow, J. H. and Woodard, H. Q. The influence of androgenic and estrogenic substances on the serum calcium in cases of skeletal metastases from mammary cancer. *J. A. M. A.*, 118: 339, 1942.
195. Herrmann, J. B. and Adair, F. E. The effect of testosterone propionate on carcinoma of the female breast with soft tissue metastases. *J. Clin. Endocrinol.*, 6: 769, 1946.
196. Adair, F. E. and Herrmann, J. B. The use of testosterone propionate in the treatment of advanced carcinoma of the breast. *Ann. Surg.*, 123: 1023, 1946.
197. Herrmann, J. B., Adair, F. E. and Woodard, H. Q. The use of testosterone propionate in the treatment of advanced carcinoma of the breast. II. The treatment of osseous metastases. *Surgery*, 22: 101, 1947.
198. Adair, F. E. The use of the male sex hormone in women with breast cancer. *Surg., Gynec. & Obst.*, 84: 719, 1947.
199. Adair, F. E. Testosterone in the treatment of breast carcinoma. *M. Clin. North America*, January, 1948.
200. Schwander, H. and Marvin, H. N. Treatment of carcinoma of the human breast with testosterone propionate: a report of five cases. *J. Clin. Endocrinol.*, 7: 423, 1947.
201. Jones, H. W., Jr. Testosterone in the treatment of advanced breast cancer. *South. M. J.*, 41: 4, 1948.
202. Davison, T. C. and Letton, A. H. Testosterone in far advanced breast cancer. *South. Surgeon*, 14: 170, 1948.
203. Walker, J. Z. Discussion on advanced cases of carcinoma of the breast treated by stilboestrol. *Proc. Roy. Soc. Med.*, 37: 731, 1944.
204. Haddow, A. The influence of carcinogenic compounds and related substances on the rate of growth of spontaneous tumors of the mouse. *J. Path. & Bact.*, 47: 567, 1938.
205. Symposium. Discussion on advanced cases of carcinoma of the breast treated by stilboestrol. *Proc. Roy. Soc. Med.*, 37: 731, 1944.
206. Haddow, A., Watkinson, J. M., Paterson, E. and Koller, P. C. Influence of synthetic oestrogens upon advanced malignant disease. *Brit. M. J.*, 2: 393, 1944.
207. Nathanson, I. T. The effect of stilbestrol on advanced cancer of the breast. *Cancer Research*, 6: 484, 1946.
208. Herrmann, J. B., Adair, F. E. and Woodard, H. Q. Effect of estrogenic hormone on advanced carcinoma of the female breast. *Arch. Surg.*, 54: 1, 1947.
209. Müller, U. Die chemische Waffe in Weltkrieg und Jetzt. Verlag Chemie, Berlin, 1935.
210. Prentiss, A. M. Chemicals in War. New York, 1937. McGraw-Hill Book Company, Inc.
211. Mandel, M. and Gibson, W. S. Clinical manifestations and treatment of gas poisoning. *J. A. M. A.*, 69: 1970, 1917.
212. Editorial. The pathology of "mustard gas." *J. A. M. A.*, 70: 1947, 1918.
213. Krumbhaar, E. B. and Krumbhaar, H. D. The blood and bone marrow in yellow cross gas (mustard gas) poisoning. *J. M. Research*, 40: 497, 1919.

214. Lynch, V., Smith, H. W. and Marshall, E. K., Jr. On dichloroethyl sulfide (mustard gas). I. The systemic effects and mechanism of action. *J. Pharmacol. & Exper. Therap.*, 12: 265, 1918–1919.

215. Gilman, A. and Philips, F. S. The biological actions and therapeutic applications of the β-chloroethyl amines and sulfides. *Science*, 103: 409, 1946.

216. Golumbic, C., Fruton, J. S. and Bergmann, M. Chemical reactions of the nitrogen mustard gases. I. The transformations of methyl-bis (β-chloroethyl) amine in water. *J. Organ Chem.*, 11: 518, 1946.

217. Golumbic, C. and Bergmann, M. Chemical reactions of the nitrogen mustard gases. II. The composition of aged unbuffered solutions of methyl-bis (β-chloroethyl) amine. *J. Organ. Chem.*, 11: 536, 1946.

218. Fruton, J. S. and Bergmann, M. Chemical reactions of the nitrogen mustard gases. III. The transformations of the ethyl-bis (β-chloroethyl) amine in water. *J. Organ. Chem.*, 11: 543, 1946.

219. Golumbic, C., Stahmann, M. A. and Bergmann, M. Chemical reactions of the nitrogen mustard gases. IV. The transformations of tris (β-chloroethyl) amine in water. *J. Organ. Chem.*, 11: 550, 1946.

220. Fruton, J. S., Stein, W. H. and Bergmann, M. Chemical reactions of the nitrogen mustard gases. V. The reactions of the nitrogen mustard gases with protein constituents. *J. Organ. Chem.*, 11: 559, 1946.

221. Fruton, J. S., Stein, W. H., Stahmann, M. A. and Golumbic, C. Chemical reactions of the nitrogen mustard gases. VI. The reactions of the nitrogen mustard gases with chemical compounds of biological interest. *J. Organ. Chem.*, 11: 571, 1946.

222. Golumbic, C., Fruton, J. S. and Bergmann, M. Chemical reactions of the nitrogen mustard gases. VII. Monosubstitution products of ethyl-bis (β-chloroethyl) amine and methyl-bis (β-chloroethyl) amine. *J. Organ. Chem.*, 11: 581, 1946.

223. Stahmann, M. A. and Bergmann, M. Chemical reactions of the nitrogen mustard gases. VIII. The oxidation of the nitrogen mustard gases by peracids. *J. Organ. Chem.*, 11: 586, 1946.

224. Stein, W. H., Moore, S. and Bergmann, M. Chemical reactions of mustard gas and related compounds. I. The transformations of mustard gas in water. Formation and properties of sulfonium salts derived from mustard gas. *J. Organ. Chem.*, 11: 664, 1946.

225. Moore, S., Stein, W. H. and Fruton, J. S. Chemical reactions of mustard gas and related compounds. II. The reaction of mustard gas with carboxyl groups and with the amino groups of amino acid and peptides. *J. Organ. Chem.*, 11: 675, 1946.

226. Stein, W. H. and Moore, S. Chemical reactions of mustard gas and related compounds. III. The reactions of mustard gas with methionine. *J. Organ. Chem.*, 11: 681, 1946.

227. Stein, W. H. and Fruton, J. S. Chemical reactions of mustard gas and related compounds. IV. Chemical reactions of β-chloroethyl-β-hydroxyethylsulfide. *J. Organ. Chem.*, 11: 686, 1946.

228. Stein, W. H., Fruton, J. S. and Bergmann, M. Chemical reactions of mustard gas and related compounds. V. The chemical reactions of 1, 2 bis (β-chloroethylthio) ethane. *J. Organ. Chem.*, 11: 692, 1946.

229. Stahmann, M. A., Fruton, J. S. and Bergmann, M. Chemical reactions of mustard gas and related compounds. VI. The chemistry of sulfonium salts related to mustard gas. *J. Organ. Chem.*, 11: 704, 1946.

230. Stahmann, M. A., Golumbic, C., Stein, W. H. and Fruton, J. S. Chemical reactions of mustard gas and related compounds. VII. The chemistry of bis (β-chloroethyl) sulfone, divinyl sulfone and divinyl sulfoxide. *J. Organ. Chem.*, 11: 719, 1946.

231. Gilman, A. Therapeutic applications of chemical warfare agents. *Federation Proc.*, 5: 285, 1946.

232. Philips, F. S. and Gilman, A. The relation between chemical constitution and biological action of the nitrogen mustards. P. 285. Approaches to Tumor Chemotherapy. American Association for the Advancement of Science, 1947.

233. Herriott, R. M. Inactivation of viruses and cells by mustard gas. *J. Gen. Physiol.*, 32: 221, 1948.

234. Houck, C. R., Crawford, B., Bannon, J. H. and Smith, H. W. Studies on the mechanism of death in dogs of the systemic intoxication by the intravenous injection of methyl-bis (β-chloroethyl) amine or tris (β-chloroethyl) amine. *J. Pharmacol. & Exper. Therap.*, 90: 277, 1947.

235. Graef, I., Karnofsky, D. A., Jager, V. B., Krichesky, B. and Smith, H. W. The clinical and pathologic effects of the nitrogen and sulfur mustards in laboratory animals. *Am. J. Path.*, 24: 1, 1948.

236. Kindred, J. E. Histologic changes occurring in the hemopoietic organs of albino rats after single injections of 2 chloroethyl vesicants; a quantitative study. *Arch. Path.*, 43: 253, 1947.

237. Cameron, G. R., Courtice, F. C. and Jones, R. P. The effects of β, β′-dichlorodiethyl methylamine hydrochloride on the blood-forming tissues. *J. Path. & Bact.*, 59: 425, 1947.

238. Anslow, W. P., Jr., Karnofsky, D. A., Jager, V. A. and Smith, H. W. The toxicity and pharmacological action of the nitrogen mustards and certain related compounds. *J. Pharmacol. & Exper. Therap.*, 91: 224, 1947.

239. Karnofsky, D. A., Graef, I. and Smith, H. W. Studies on the mechanism of action of the nitrogen and sulfur mustards *in vivo*. *Am. J. Path.*, 24: 275, 1948.

240. Rose, H. M. and Gellhorn, A. Inactivation of influenza virus with sulfur and nitrogen mustards. *Proc. Soc. Exper. Biol. & Med.*, 65: 83, 1947.

241. Spurr, C. L. Influence of nitrogen mustards on the antibody response. *Proc. Soc. Exper. Biol. & Med.*, 64: 259, 1947.

242. Chen, G. The effect of methyl-bis (β-chloroethyl) amine on Tryponosoma equiperdum. *J. Infect. Dis.*, 82: 133, 1948.

243. Gillette, R. and Bodenstein, D. Specific developmental inhibitions produced in amphibian em-

bryos by a nitrogen mustard compound. *J. Exper. Zool.*, 103: 1, 1946.

244. Bodenstein, D. The effects of nitrogen mustard on embryonic amphibian development. I. Ectodermal effects. *J. Exper. Zool.*, 104: 311, 1947.
245. Friedenwald, J. S., Buschke, W., Scholz, R. O. and Moses, S. J. Some effects of sulfur and nitrogen mustards on cell nuclei in mammalian cornea. P. 358. Approaches to Tumor Chemotherapy. American Association for the Advancement of Science, 1947.
246. Staff of the Wilmer Institute. Studies on the physiology, biochemistry, and cytopathology of the cornea in relation to injury by mustard gas and allied toxic agents. *Bull. Johns Hopkins Hosp.*, 82: 81, 1948.
247. Auerbach, C. and Robson, J. M. Chemical production of mutations. *Nature, London*, 157: 302, 1946.
248. Auerbach, C., Robson, J. M. and Carr, J. G. The chemical production of mutations. *Science*, 105: 243, 1947.
249. Stahmann, M. A. and Stauffer, J. F. Induction of mutants in Penicillium notatum by methyl-bis (β-chloroethyl) amine. *Science*, 106: 35, 1947.
250. Horowitz, N. H., Houlahan, M. B., Hungate, M. G. and Wright, B. Mustard gas mutations in Neurospora. *Science*, 104: 233, 1946.
251. Bodenstein, D. and Kondritzer, A. A. The effect of nitrogen mustard on nucleic acids during embryonic amphibian development. *J. Exper. Zool.*, 107: 109, 1948.
252. Boyland, E. The pharmacology of chloroethylamines. *Biochem. Soc. Symposium*, 2: 61, 1948.
253. Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A. and McLennan, M. T. Nitrogen mustard therapy. Use of methyl bis (β-chloroethyl) amine hydrochloride and tris (β-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. *J. A. M. A.*, 132: 126, 1946.
254. Burchenal, J. H. The newer nitrogen mustards in the treatment of leukemia. *Radiology*, 50: 494, 1948.
255. Wintrobe, M. M., Huguley, C. M., Jr., McLennan, M. T. and de Carvalho Lima, L. P. Nitrogen mustard as a therapeutic agent for Hodgkin's disease, lymphosarcoma and leukemia. *Ann. Int. Med.*, 27: 529, 1947.
256. ApThomas, M. I. R. and Cullumbine, H. Nitrogen mustards in Hodgkin's disease, report on 21 cases and 4 other reticuloses. *Lancet*, 1: 899, 1947.
257. Osborne, E. D., Jordon, J. W., Hoak, F. C. and Pschierer, F. J. Nitrogen mustard therapy in cutaneous blastomatous disease. *J. A. M. A.*, 135: 1123, 1947.
258. Karnofsky, D. A., Craver, L. F., Rhoads, C. P. and Abels, J. C. An evaluation of methyl bis (β-chloroethyl) amine hydrochloride and tris (β-chloroethyl) amine hydrochloride (nitrogen mustards) in the treatment of lymphomas, leukemias and allied disorders. Approaches to tumor chemotherapy. P. 319. American Association for the Advancement of Science, 1947.
259. Jacobson, L. O., Spurr, C. L., Barron, E. S. G., Smith, T., Lusbaugh, C. and Dick, G. F. Nitrogen mustard therapy—studies on the effect of methyl bis (β-chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system. *J. A. M. A.*, 132: 263, 1946.
260. Spurr, C. L., Jacobson, L. O., Smith, T. R. and Barron, E. S. G. The clinical application of methyl bis (β-chloroethyl) amine hydrochloride to the treatment of lymphomas and allied dyscrasias. Approaches to Tumor Chemotherapy. P. 306. American Association for the Advancement of Science, 1947.
261. Karnofsky, D. A. The nitrogen mustards and their application in neoplastic disease. *New York State J. Med.*, 47: 992, 1947.
262. Rhoads, C. P. Nitrogen mustards in the treatment of neoplastic disease. Official statement. *J. A. M. A.*, 131: 656, 1946.
263. Wintrobe, M. M., McLennan, M. T., Huguley, C. M., Jr. Clinical experiences with nitrogen mustard therapy. Approaches to Tumor Chemotherapy. P. 347. American Association for the Advancement of Science, 1947.
264. Wilkinson, J. F. and Fletcher, F. Effect of β-chloroethyl amine hydrochloride in leukemia, Hodgkin's disease, and polycythemia vera. Report of 18 cases. *Lancet*, 2: 540, 1947.
265. Bortz, D. W. and Haden, R. L. Nitrogen mustard therapy. Report of 16 cases thus treated. *Cleveland Clin. Quart.*, 14: 218, 1947.
266. Henstell, H. H., Tober, J. N. and Newman, B. A. The influence of nitrogen mustards on mycosis fungoides. Observations relating its effect to the reticulo-endothelial system. *Blood*, 2: 564, 1947.
267. Snider, G. E. Treatment of Boeck's sarcoid with nitrogen mustard. A preliminary report. *South. M. J.*, 41: 11, 1948.
268. Cowdry, E. V. The Fourth International Cancer Research Congress. St. Louis, September 2–7, 1947. *J. A. M. A.*, 135: 1067, 1947.
269. Philpott, O. S., Woodburne, A. R. and Waldriff, G. A. Nitrogen mustard in the treatment of mycosis fungoides. *J. A. M. A.*, 135: 631, 1947.
270. Hettig, R. A. Result of methyl bis (β-chloroethyl) amine hydrochloride therapy. A preliminary report of a nitrogen mustard. *J. Lab. & Clin. Med.*, 32: 1431, 1947.
271. Rhoads, C. P. Recent advances in treatment of cancer. *J. A. M. A.*, 136: 305, 1948.
272. Taffel, M. Experiences in treatment of neoplastic disease with nitrogen mustard. *Yale J. Biol. & Med.*, 19: 441, 1947.
273. Hofmeyr, H. O. Clinical experiences with nitrogen mustards in Hodgkin's disease. *South African M. J.*, 21: 195, 1947.
274. Sherry, M. Nitrogen mustards in the treatment of Hodgkin's disease and lymphosarcoma. *South. M. J.*, 41: 118, 1948.
275. Faloon, W. W. and Gorham, L. W. Clinical experience with nitrogen mustard. *New York State J. Med.*, 48: 612, 1948.
276. Craver, L. F. The nitrogen mustards: clinical use. *Radiology*, 50: 486, 1948.

277. CRAVER, L. F. Lymphomas and leukemias. *Bull. New York Acad. Med.*, 23: 79, 1948.
278. SPURR, C. L., SMITH, T. R. and JACOBSON, L. O. Chemotherapy in human lymphomas, leukemias, and allied disorders of the hemopoietic system. *Radiology*, 50: 387, 1948.
279. JACOBSON, L. O., SPURR, C. L., SMITH, T. R. and DICK, G. J. Radioactive phosphorus and alkylamines in the treatment of neoplastic and allied diseases of the hemopoietic system. *M. Clin. North America*, 31: 3, 1947.
280. ALPERT, L. K. and PETERSON, S. S. The use of nitrogen mustard in the treatment of lymphomata. *Bull. U. S. Army M. Dept.*, 7: 187, 1947.
281. WINTROBE, M. M. and HUGULEY, C. M. Nitrogen mustard therapy for Hodgkin's disease. *Cancer*, 1: 357, 1948.
282. SMITH, T. R., JACOBSON, L. O., SPURR, C. L., ALLEN, J. G. and BLOCK, M. H. A coagulation defect produced by nitrogen mustard. *Science*, 107: 474, 1948.
283. BOYLAND, E., CLEGG, J. W., KOLLER, P. C., RHODEN, E. and WARWICK, O. H. The effects of chloroethylamines on tumors, with special reference to bronchogenic carcinoma. *Brit. J. Cancer*, 2: 17, 1948.
284. KARNOFSKY, D. A. Personal communication.
285. KIERLAND, B. R., WATKINS, C. H., and SCHULLENBERGER, C. C. The use of nitrogen mustard in the treatment of mycosis fungoides. *J. Invest. Dermat.*, 9: 195, 1947.
286. KARNOFSKY, D. A. Chemotherapy of neoplastic disease. *New England J. Med.*, 239: 226, 260, 299, 1948.

Seminars on Congestive Failure

The Role of the Cardiac Output in the Mechanisms of Congestive Heart Failure*

EUGENE A. STEAD, JR., M.D.

Durham, North Carolina

SYMPTOMS of heart disease are of two types: (1) those caused by failure of the heart as a pump and (2) those caused by local ischemia of heart muscle. It is common clinical knowledge that the patient may have angina pectoris without congestive failure or congestive failure without angina. In the first instance the heart responds normally to exercise with an increase in cardiac output. A local area of the heart muscle increases its metabolism without being able to increase its blood supply proportionately because of coronary artery disease. Substances which accumulate in working muscles poorly supplied with blood stimulate sensory nerve endings and the subject is conscious of substernal pain. The heart pumps the required amount of blood for the needs of the body and pain stops further exertion. In the second instance, the heart does not perform its work well as a pump. Symptoms from this cause limit exertion before an area of local ischemia occurs. The picture is that of congestive heart failure rather than angina pectoris.

Congestive heart failure differs from the circulatory failure commonly produced by various means in the laboratory in that the arterial pressure is well maintained and that the condition lasts for days, weeks and years. The symptoms of congestive failure can be divided into two groups: (1) those resulting from the inability of the heart to increase its output normally in response to increased peripheral need for blood. The muscular weakness of congestive failure is a familiar example. (2) Those resulting from congestion and edema of the lungs, liver, skin and other organs. There has been no controversy about the first group of symptoms. There has been little agreement about the chain of events leading to congestion and edema.

It has seemed logical to relate the congestion and edema of the various organs to the failure of the heart as a pump. Accordingly, the cardiac output has been investigated in normal subjects and in those with congestive heart failure. The methods in which a foreign gas has been used have been largely replaced today by the method of right heart catheterization utilizing the Fick principle. This technical advance has allowed the study of patients who were too ill to cooperate actively in the breathing maneuvers required by the foreign gas methods.

As measured by the technic of right heart catheterization, the cardiac output in normal subjects under basal conditions is around 3.3 L. per minute per sq. M. of body surface.[1] The spread of values for normal, relaxed, fasting subjects is considerable, ranging from 2.3 to 4.1 L. The output is increased by apprehension, exercise, sudden lowering of peripheral resistance, intake of food and administration of epinephrine. The mechanisms for increasing the cardiac output are complex and have not been clearly defined in man.[2] Changes in right atrial pressure do not cause the consistent changes in cardiac output which are seen in the heart-lung preparation. The increased cardiac output of

* From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

anemia, thyrotoxicosis, apprehension and sudden lowering of peripheral resistance are not accompanied by increase in right atrial pressure.

The cardiac output is decreased by motionless standing, by large hemorrhage and by myxedema. Lowering of the mean right atrial pressure by 3 to 4 cm. of water, by venesection or by pooling of blood in the extremities does not cause a consistent fall in cardiac output.[3]

As measured by the Fick principle, the cardiac output is determined by two factors: (1) the arterial-mixed venous oxygen difference and (2) the oxygen consumption per minute. A rise in metabolism without an increase in A-V oxygen difference or a decrease in A-V difference without a fall in metabolism both indicate a rise in cardiac output. In apprehension the decrease in A-V oxygen difference and a less marked rise in oxygen consumption give a high output.[1] In light exercise a rise in oxygen consumption and a slight increase in A-V oxygen difference indicate a high output.[4]

In congestive heart failure the resting cardiac output, as measured by the foreign gas methods and by the direct Fick principle, is usually decreased.[5] This decrease is more striking if considered in relation to the two measurements from which the cardiac output is derived. Fewer liters of blood per minute are pumped by the heart and more oxygen is removed from each liters by the tissues to compensate for slow blood flow. For any given level of anxiety or work the patient with *uncomplicated* congestive failure has an A-V oxygen difference greater than normal.[4,5] The stimulus of exercise may raise the cardiac output somewhat above the resting level. That the response is abnormal is shown by the fact that at any level of oxygen consumption the A-V oxygen difference is wider than in a normal subject with an equal oxygen consumption. In spite of the fact that the majority of patients with congestive heart failure show these findings, there are some who show a normal cardiac output and in a few the output is elevated. Because of these exceptions the question arises: Is a reduction in cardiac output an essential part of the picture of congestive failure?

Patients with thyrotoxicosis, anemia and arteriovenous fistula have abnormally high values for the resting cardiac output.[2] It is not surprising that when the heart fails in the presence of these complicating factors, the signs of congestive failure are present before the circulation falls below that found in a resting normal subject of the same size. The output, although high in the terms of the normal, is insufficient for the demands created by the physiologic or pathologic circumstances; and signs of circulatory insufficiency develop even though the output is still considerable.

Probably too much emphasis has been placed on the development of congestive failure with an output above the resting level. This actually seems to be the rule rather than the exception in the first bout of congestive failure which comes on slowly. The patient notices fatigue, dyspnea and a low urine output during the day. At night he is awakened several times to void and notes that the night urine is increased in amount. At this stage of failure the cardiac output is found to be normal at rest. During his daily activity when the signs of congestion are developing, the cardiac output is increased above the level of rest but not to the degree required by the activity; and the signs of congestion develop in spite of an output above the resting level. The fact that the output although high is not as high as is needed is shown by the wide A-V oxygen difference.

According to this interpretation, the congestive phenomena of heart failure occur whenever over a long period of time the cardiac output is insufficient to supply the organs and tissues of the body with the optimal amount of blood. The optimal amount of blood will vary with activity and disease. In thyrotoxicosis in failure the output will be high because of the increased oxygen consumption; in beriberi it will be high because of the peripheral vasodilatation caused by the metabolic defect. In

either instance congestive failure will develop whenever organ blood flow falls below the level required by the altered metabolism. In heart failure the blood flow to all organs is probably slightly below the optimal level, but that through the kidney is particularly decreased. The fall in renal blood flow eventually reaches the point where the glomerular filtrate is reduced and abnormal retention of sodium occurs.

The massive edema so characteristic of congestive failure occurs only when sodium chloride and water are retained by the kidneys. This does not mean that pulmonary edema cannot occur except by the renal mechanism. It does mean that edema associated with gain of weight requires a renal mechanism. In the sudden pulmonary edema caused by a massive myocardial infarct of the left ventricle there is no time for sodium retention. The blood is forced into the lungs by the right heart and cannot be removed by the left. Rapid and frequently fatal pulmonary edema may develop. A consideration of this problem brings up the question of failure of the right or left ventricles as contrasted to failure of both chambers of the heart.

The available data favor the view that two factors are important in the pulmonary congestion of congestive failure: (1) left ventricular failure; (2) retention of sodium and water by the kidneys.

Clinical observation teaches us that the lungs are involved early in heart failure caused by hypertension, luetic aortitis and coronary artery disease. The lungs contain too much blood and water, as shown by dyspnea, decreased vital capacity, increased circulation time and high pulmonary arterial pressure. These symptoms of pulmonary congestion usually precede the onset of generalized pitting edema and the rise in systemic venous pressure. The physiologic and pathologic evidence would favor the view that the lungs are engorged because at times the right ventricle pumps blood into the lungs at a faster rate than the left ventricle pumps it out. This increases the pulmonary capillary pressure and causes a large amount of fluid retained by the kidney to localize in the lungs. Where does this blood come from which the right ventricle pumps into the lungs? It is the blood pumped to it by the left ventricle plus the amount of blood that the right ventricle receives from the systemic circulation by a combination of two mechanisms: (1) Recent work has demonstrated that the right side of the heart can increase its output in the face of a moderate fall in right atrial pressure.[2] Thus, when appropriately stimulated the right side of the heart may deliver blood into the lungs without a corresponding increase in output of the left ventricle by allowing the right atrial pressure to fall. (2) Active constriction of the systemic venous bed can deliver to the right side of the heart a quantity of blood which is not dependent on the output of the left ventricle. Thus, physiologic, pathologic and clinical data support the concept that backing up of blood behind a failing left ventricle is a common occurrence in the usual types of heart disease.

The concept of right ventricular failure developing later in the course of heart disease with backing up of blood behind the right side of the heart because of right ventricular failure is much harder to visualize. Clinical observation shows that as heart failure advances peripheral edema and a rise in systemic venous pressure occur. Consider the quantitative aspects of the problem. The blood available for backing up behind the right side of the heart is that pumped out by the left ventricle plus that normally available in the systemic venous bed. The blood pumped out by the left ventricle is that delivered to it by the right side of the heart plus that which might be delivered to the left ventricle by active pulmonary venous constriction. It is doubtful if the lungs can deliver enough blood to the left side of the heart to flood the peripheral circulation. Further doubt is thrown on the thesis of right ventricular failure because of the clinical evidence that left ventricular failure continues to persist as the dominant lesion even after edema and

increased peripheral venous pressure occur. If such a person is made free of peripheral edema by sodium restriction in the diet, the abnormalities in the pulmonary circulation will persist although there is no detectable edema and the right atrial pressure is normal.

It would appear that in the usual patient with heart failure the concept of flooding of the lungs from left ventricular failure is a sound explanation for the pulmonary congestion, but that the available evidence is against the flooding of the systemic circulation by right ventricular failure as a cause of the increased venous pressure and systemic edema.

The picture of left ventricular failure uncomplicated by sodium retention is seen most commonly in patients with massive infarction of the left ventricle. Blood enters the lung from the right ventricle; the damaged left ventricle must let it remain there. Massive pulmonary edema develops rapidly without an increase in body weight. In the more common types of left ventricular failure the picture does not seem quite as simple. Although pitting edema is absent, the patient has usually retained a few pounds of fluid. Furthermore, the administration of a mercurial diuretic frequently lessens the edema without any detectable improvement in left ventricular function. Conversely, a high salt intake makes the dyspnea worse. These clinical considerations point to the conclusion that while a rise in pulmonary capillary pressure alone may cause pulmonary edema, this rise in pulmonary capillary pressure is commonly accompanied by retention of salt and water by the body, and that these two factors together are responsible for the dyspnea and orthopnea of left ventricular failure.

We now return to the original question: Is the disproportion between the output of the two ventricles responsible for the picture of congestive failure without regard to the absolute level of the cardiac output? The answer is both yes and no. The lungs can be flooded from the systemic circulation and this can conceivably occur with a level of output of the left ventricle adequate to supply satisfactorily all the needs of the body for blood. In most instances, the picture of backing up of blood behind the left ventricle appears to be accompanied by a simultaneous retention of salt and water. The flooding of the systemic circulation by the lungs seems unlikely, and the increased systemic venous pressure and peripheral edema in the usual patient with heart failure cannot be explained by backing up of blood behind a failing right ventricle.

The increase in systemic venous pressure in patients with heart failure has frequently been interpreted as a compensatory mechanism for maintaining the output of a failing heart. Clinical evidence to support this interpretation has never been very convincing. The situation differs from the heart-lung preparation in that marked chronic dilatation of the heart chambers and hypertrophy of the muscle have occurred. A dilated right heart apparently fills completely over a wide range of venous pressures. Although direct observations are lacking, it seems likely that the same is true for the left ventricle. The primary defect seems to be in ventricular emptying. Systole leaves a large quantity of residual blood in the heart. During diastole the ventricle fills to full capacity and wide variations in right atrial pressure have little effect on output. In patients with chronic fixed failure the venous pressure varies with the sodium intake.[6] Studies on these subjects show no beneficial effects of a high right atrial pressure.

It is certainly true that the heart of a patient with failure does not always respond to a given stimulus in the same way as it does in a normal subject. Exercise in the normal subject causes the output to rise. In certain patients with congestive failure the output may fall with exercise.[4] In normal subjects apprehension causes a rise in cardiac output; in the cardiac it may cause a fall. In the normal subject venesection causes no consistent change in out-

put;[3] in the patient with pulmonary edema from heart failure venesection causes a rise in cardiac output.[7,8] In these examples one sees that the failing heart, when pushed too far, becomes even sicker and the output falls. The author believes that the increased load on the circulation may cause a further decrease in the ability of the heart to empty. Lessening of the load by sedation or rest or relieving the intense reflex activity of pulmonary edema by venesection, tourniquets or mercurial diuretics may increase the ability of the heart to empty. According to this conception the progressive failure of the heart occurs from fatigue, and overdistention of the ventricular muscles by a high venous pressure is not a fundamental part of the failure. Conventional physiology attributes the further failure of the heart with exercise or pulmonary edema to a rise in venous pressure and overdistention of the heart. Time will determine which interpretation is correct.

The heart in failure responds to digitalis by an increase in output. This is accomplished by a more complete emptying of the heart in systole. The increase in output may be accompanied by a striking or insignificant fall in right atrial pressure. In certain borderline patients in whom the cardiac output is at the lower limit of normal, a significant rise with digitalis demonstrates that the output is not optimal for that particular patient.

SUMMARY

If one measures the cardiac output at rest in patients with failure, the following combinations will be found:

1. Cardiac output low with failure remains low when symptoms are relieved by sodium restriction or continued use of diuretics. These are the usual findings in fixed intractable heart failure.

2. Cardiac output low with failure increases with administration of digitalis or when such complications as pulmonary infarction clear up. This condition does not require salt restriction or diuretics when activity is reduced by bed rest.

3. Cardiac output normal with failure remains normal on compensation. Decompensation develops with increased activity. Cardiac output adequate for diuresis at rest; symptoms at time of study because of waterlogging of body which persists until diuresis is completed.

4. Cardiac output high with failure falls when the stimulus for an increased output is removed. This combination may be shown (1) by restless, apprehensive, dyspneic patients whose output is adequate for rest but inadequate for mild exertion; and (2) by patients with hyperthyroidism, anemia, arteriovenous fistula, patent ductus arteriosus, beriberi and certain infections.

REFERENCES

1. Stead, E. A., Jr., Warren, J. V., Merrill, A. J. and Brannon, E. S. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. *J. Clin. Investigation.*, 24: 326–331, 1945.
2. Stead, E. A., Jr. and Warren, J. V. Cardiac output in man. An analysis of the mechanisms varying the cardiac output based on recent clinical studies. *Arch. Int. Med.*, 80: 237–248, 1947.
3. Warren, J. V., Brannon, E. S., Stead, E. A., Jr. and Merrill, A. J. The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. *J. Clin. Investigation*, 24: 337–344, 1945.
4. Hickam, J. B. and Cargill, W. H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J. Clin. Investigation*, 27: 10–23, 1948.
5. Stead, E. A., Jr., Warren, J. V. and Brannon, E. S. Cardiac output in congestive heart failure. *Am. Heart J.*, 35: 529–541, 1948.
6. Warren, J. V. and Stead, E. A., Jr. Fluid dynamics in chronic congestive heart failure. *Arch. Int. Med.*, 73: 138–147, 1944.
7. McMichael, John. Personal communication.
8. Unpublished observations from this laboratory.

Conference on Therapy

Household Poisonings

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. HARRY GOLD: The conference today is on the subject of household poisons. It is not very easy to draw a line around the group of household poisons as it seems to include many of the poisons used in industry, many of the medicines found in drug stores and chemicals found in the grocery stores, paint stores and others. I suppose that the best we can do is to consider a few of the more common poisons and perhaps some of the more interesting.

Any one physician may not see a great many cases of poisoning in the home, but in the aggregate the number of cases is very large. In one report, made in 1934 by Aikman of Rochester, attention was called to the fact that 1 per cent of all the children in the Strong Memorial Hospital were admitted for some form of poisoning. About one-quarter of all those cases were accidental poisonings and about one-half were therapeutic poisonings. That one of every one hundred children in a hospital was there because of poisoning indicates that the topic of the conference today is one of major importance. Perhaps in the course of the discussion we may learn how these matters stand in the New York Hospital.

The major proportion of household poisonings occur in children. There is a report to the effect that in 1929 in the United States there were 530 deaths due to accidental poisoning in children under five. The numbers declined all the way down to fifty cases during the next five-year age period. It seems that in the age group up to five there is a population of individuals who go rummaging about, picking up medicines and swallowing things they have no business to be swallowing. The drugs and chemicals involved in these poisonings cover a very wide field. In one report listing 158 cases of fatal poisonings in a five-year period in children under five years of age in New York State there were forty-five different substances listed. One poison stood out in that group. Would anybody venture a guess?

STUDENT: Camphor?

DR. GOLD: No.

STUDENT: Rat poison?

DR. GOLD: No.

STUDENT: Lead?

DR. GOLD: No.

STUDENT: Phosphorus?

DR. GOLD: No.

DR. JANET TRAVELL: Phenolax?

DR. GOLD: No.

STUDENT: Aspirin?

DR. GOLD: No.

STUDENT: Alcohol?

DR. GOLD: No. You must remember these were all individuals under five years of age.

STUDENT: How about iodine?

DR. GOLD: No.

DR. TRAVELL: Strychnine?

DR. GOLD: That is correct. About one-half of all the cases of fatal poisonings in this group, namely, 75 of the 158, were due to strychnine. There was no close second in the entire list. The remaining eighty-three cases were caused by forty-four different substances. The cases of strychnine poisoning were due to the use of cathartic and "tonic" pills. The cathartic pills, containing

aloin, strychnine and belladonna, the so-called A. S. et B. pills, and those containing in addition resin of podophyllum and extract of cascara, or the so-called Hinkle's pills, were the chief offenders. Incidentally, the more recent edition of the National Formulary (1946) has eliminated strychnine from the Hinkle's pills but has doubled the dose of strychnine in the A. S. et B. pill, from 1/120 to 1/60 gr. These are very tiny pills and if a child about five years of age helps himself to about ten or fifteen of these innocent looking pellets, he develops severe strychnine poisoning and may die with convulsions.

We receive fairly frequent inquiries in relation to cases of poisoning. It is usually a telephone call for suggestions. I am in the habit of making a memo of the circumstances and placing it in a folder. It might be interesting to have a look at a few of these at random. This may give us some idea of the nature of the problem in a case of household poisoning.

Here is a case of atropine poisoning. The record is dated 1935 but there have been additional similar ones since. Someone in the family received atropine drops for use in the eyes. The two year old baby helped itself to the bottle and, according to the account, swallowed the contents, about 20 cc. of a 1 per cent solution of atropine sulfate. The doctor arrived an hour and one-half later and found the baby hot, flushed, restless, conscious, with dilated pupils and a fever of 102°F. He promptly washed the stomach and brought the patient to the hospital. In the next few hours, because the condition of the patient seemed unchanged, treatment was instituted. The baby received a dose of 10 mg. per Kg. of amytal sodium intramuscularly. From that point on the real trouble began. The patient quite promptly went into a very deep stupor and then coma, with very shallow respiration. The pulse became feeble and cyanosis developed. The Drinker respirator was installed for any possible emergency. Nothing happened. The following day the child woke up and seemed to be well on the way to recovery. Here is a case which started out as a possible accidental poisoning by atropine but ended up as a therapeutic poisoning with amytal sodium. The baby received the equivalent of about 12 gr. (0.8 Gm.) of amytal, normally given an adult. Such a dose is not likely to prove fatal but produces a fairly high degree of depression in a great many people. The dose of atropine presents a point of interest. It is commonly stated that the fatal dose of atropine for children is about 10 mg. and for adults about 100 mg. I am not aware of any proof of deaths in either children or adults from such doses. There is a statement in the literature to the effect that the smallest recorded dose which proved fatal was 95 mg. in a child and 130 mg. in an adult. On this basis the patient took about twenty times the fatal dose of atropine. I believe that the dose of atropine stated in the literature to be fatal is much too small. From experience in animals atropine produces pronounced symptoms after very small doses due to blocking of the autonomic nervous system, but these actions are not the ones which cause the fatality and the fatal effects require massive doses. In a cat, for example, a small fraction of a mg. per Kg. blocks the cardiac vagus, but the fatal dose is of the order of 50 mg. per Kg. Humans may be much more sensitive to the fatal action of atropine, but indications from the isolated reports of atropine poisoning are that in humans also a wide gap exists between the dose which causes very disturbing symptoms and the one which causes death. For example, a 10 mg. dose of atropine is apt to produce delirium but recovery is reported from a dose as high as 500 mg. In the case in question there also remains the possibility that the child might not have swallowed all the solution that disappeared from the bottle for a 1 per cent solution of atropine is fairly bitter.

I cite this case merely as an illustration of a fact which I think applies to household poisonings in general, namely, the danger of treatment. When one does not know what is best to do, it is probably best to do noth-

ing. In the reported cases of poisoning with atropine, maniacal delirium frequently occurs and that has been controlled by a barbiturate. In the case to which I have just referred, however, there was no delirium and, therefore, no indication for use of a large dose of amytal.

Here is the record of another inquiry. A baby was having its temperature taken by rectum. The thermometer broke and the mercury remained in the rectum. What should be done? What is the chance of serious poisoning from mercury? I have two additional inquiries of a similar nature, but in these the children bit off the bulb of the thermometer and swallowed the mercury. All of these queries were answered in the same way: Let them be and do nothing about it. The average clinical thermometer contains about 1 Gm. of mercury. There was a time when as much as 100 to 500 Gm. of metallic mercury was given orally for the treatment of ileus. In rare cases this dose caused death. There is no doubt of the fact that some absorption takes place from metallic mercury given in bulk but the amount absorbed from a dose given in that way must be very small. There is the account of a man who attempted suicide by injecting 2 cc. or 27 Gm. of metallic mercury into his vein; he developed some diarrhea but lived about ten years. It is otherwise when the metallic mercury is finely divided. It used to be a fairly common practice to give children as much as 100 mg. of metallic mercury in the form of a dose of 0.25 Gm. of mercury with chalk in a capsule for the treatment of syphilis. These experiences suggest that the mercury released from the broken bulb of the thermometer may be ignored with impunity. This was done in the three cases to which I have referred and there were no reasons to regret it.

I have a memorandum on a telephone call from a pediatrician regarding the possibility of poisoning from matches. The child was playing with a box of safety matches and chewed off the tips. Precisely how many had been chewed he did not know but he was informed that it was the contents of a nearly full small box. The problem related to the possibility of phosphorus poisoning. He was reassured to learn that to get into difficulties from that adventure the child would have had to consume the box rather than the matches.

The friction match which can be struck anywhere was originally tipped with yellow phosphorus and fifteen or twenty tips might provide a fatal dose of phosphorus. But in the safety match the phosphorus is on the striking surface of the box and even this in present day matches no longer contains the highly toxic, yellow phosphorus but the unabsorbable red phosphorus. The latter is relatively non-toxic although some contamination with yellow phosphorus is a source of danger. Incidentally, even the ordinary match, which may be struck anywhere, is now relatively innocuous because the non-toxic phosphorus sesquisulfide has replaced the yellow phosphorus.

There is here an inquiry regarding a barbiturate. A baby, seven months old, got his hands on a capsule of 0.2 Gm. of amytal sodium and swallowed it about thirty minutes previously. There are, at this time, no appreciable effects. What should be done? The suggestion was made to empty the stomach or wash it. This was not imperative. It would only result in eliminating the protracted period of stupor or shortening the period of deep sleep. Since the total dose represented only about 30 mg. per Kg., the risk of fatal barbiturate poisoning was negligible. Considerably larger doses used to be extensively employed to induce anesthesia for surgical operations. This is a good example of poisoning in which, as is very often the case, the patient does well without treatment.

We recently had an inquiry about moth balls in connection with a child who had eaten some. Many materials may be involved in poisoning by moth balls or other moth repellent articles, namely, camphor, naphthalene and paradichlorobenzene. Paradichlorobenzene is the compound now most widely used in the various forms of

moth repellent materials. Exposure to its fumes over long periods of time causes poisoning, but by oral administration the compound is relatively innocuous. In the dog feeding of 1.0 Gm. per Kg. daily (equivalent to about 60 Gm. for an average adult) for a long period of time has been found to produce no toxic effects. This compound appears in the home in such forms as nuggets, flakes, cakes and pellets. The smaller nuggets weigh about 0.25 Gm. and the larger ones as much as 7 Gm. Should an infant or a very young child consume three or four of the larger nuggets, it is unlikely that serious poisoning would occur. Some moth repellent materials contain naphthalene or a mixture of naphthalene and paradichlorobenzene. We recently examined a trade box of moth balls which contained only naphthalene, each ball weighing approximately 2.5 Gm. Naphthalene is more toxic than paradichlorobenzene. It is used in doses of 0.5 Gm. in the treatment of oxyuris infestations. Death has been reported in a child from as little as 2 Gm., but the fatal dose of naphthalene for most cases is considerably larger. It seems unlikely that the consumption of a naphthalene moth balls by an infant or young child would prove serious. The few recorded cases of naphthalene poisoning refer to such symptoms as abdominal cramps, nausea and vomiting, motor instability and irritation of the urinary tract with burning in the urethra and urgency. It is apparently also damaging to the liver and kidney, giving rise to jaundice and albuminuria. The cases of poisoning by paradichlorobenzene in individuals exposed to the fumes for long periods of time are characterized by injury to the liver and by cataracts.

Camphor is now rarely found in moth balls although these are sometimes referred to as camphor balls. Camphor cakes are still available and used as moth repellents. It is the experience that camphor taken by mouth may cause dramatic and threatening symptoms but most patients recover. We shall refer to camphor again presently.

A word about the general problem of moth repellent articles is in order at this point. A doctor recently telephoned me about a child that had taken a quantity of a moth repellent known as Expello. We examined several brands of moth repellent nuggets with the label stating clearly that these represented paradichlorobenzene. However, the can of Expello gave no indication of the nature of the contents. The pellets in this can had a somewhat different smell from those labeled paradichlorobenzene. That threw us off the track although we were aware of the fact that the most common moth repellents are chiefly paradichlorobenzene. The manufacturer of Expello is in New Hampshire and was, therefore, not readily accessible to us, but a label was inscribed on the can stating that it was guaranteed by the Good Housekeeping Institute. We, therefore, contacted them for information about this material. They gave us the information, namely, that Expello represents paradichlorobenzene. There is something wrong about having such a material which is always so accessible to children in the household without the name of the chemical clearly stated on the container. It is hardly to be expected that the physician will be familiar with the chemical composition of all moth repellent articles under proprietary names which give no indication of the nature of the product. It would have spared the family a good deal of anguish and the physician no end of trouble if the name paradichlorobenzene had appeared somewhere on the label for even if this compound might not have caused any harm by reason of its low toxicity, the physician would be forced to take measures in treatment which would have been unnecessary had the name of the compound been known to him. Another disturbing aspect of this experience was the fact that of the three cans in our possession the only one which failed to disclose the contents was the one bearing the seal of the Good Housekeeping Institute. I presume that housewives take the seal of the Good Housekeeping Institute seriously and are likely

to prefer articles bearing its name. Under the circumstances I wonder whether the Good Housekeeping Institute ought not to recognize a moral obligation in the matter and insist on the chemical name appearing on the container of articles which may, rightly or wrongly, find their way into the mouth of a youngster rummaging about in the house. A person in charge of these matters in the Institute informed me that the label was entirely adequate within the meaning of the law and that this moth repellent, Expello, did not fall in the class of so-called "economic poisons." We should take cognizance of the fact that a substance which is not classed as a so-called economic poison is not necessarily non-toxic. The criteria for an economic poison merely differentiate between those articles which take small doses to kill and those which require somewhat larger doses to kill. For example, in an extreme case, if the average lethal dose per Kg. were 49 mg., it would be classed as an economic poison, whereas if the average lethal dose were 51 mg., the article would stand outside of the class of economic poisons. I think this is not an improper place to suggest that something be done to insure that when a doctor is called upon to treat a possible case of poisoning by a common household material, the label on the container inform him of the exact nature of the chemical and the amount of it that is present in the preparation. Without that information, he is often quite helpless.

Camphorated oil is sometimes mistaken for castor oil and it might be well therefore to know something about the toxicity of camphorated oil. Camphor is a convulsant but it is very rapidly eliminated so that even after a fairly violent convulsion the individual is likely to recover. While there are a great many cases of camphorated oil poisonings, the number of deaths is very low even in cases in which violent convulsions have occurred. Camphorated oil is a 20 per cent solution of camphor in oil, and the smallest oral doses of camphor which are on record as causing death are of the order of 1.5 Gm. That would make about two teaspoonfuls of camphorated oil. There have been instances of mass poisoning from camphorated oil. In one series each of some twenty children received from 1 to 1.5 tablespoonfuls of camphorated oil. Most of them developed convulsions but they all recovered.

Infants and children seem to have little trouble in getting hold of a bottle or can of kerosene or gasoline. Also they do not seem to have any particular aversion to drinking it. There are still places in the country in which kerosene is used in doses of a few cc. for the treatment of bronchitis and colds. A considerable number of cases of poisoning are encountered. There are recoveries from as much as 125 cc. of kerosene and deaths from as little as 30 cc. There is the case of an adult who recovered from 750 cc. There is not enough information to be certain whether kerosene or non-leaded gasoline is more toxic. The course of kerosene poisoning is very rapid. Effects appear within a few minutes with gastrointestinal symptoms (vomiting, diarrhea, abdominal cramps) and central nervous system symptoms (coma, convulsions). About 5 to 10 per cent of the patients die and this takes place in less than twenty-four hours. The remainder seem to recover completely and fairly promptly. It is fairly safe to assume that the patient who is still alive on the day after a dose of kerosene is likely to recover. It behaves in many respects like a volatile anesthetic. The lungs seem to be involved in a large proportion of the cases and such a case may be mistaken for one of primary pneumonia. It is not certain how the lungs become involved, whether by excretion of the volatile agent through the lungs or aspiration during vomiting. It is noteworthy that in animal experiments the fatal dose by stomach is about ten times that by intratracheal injection. This may indicate rapid absorption from the pulmonary bed or marked inflammatory reaction to the high concentration. It is obvious that the stomach should be washed if the time interval suggests that any appreciable amount may still be there and special care needs to be taken

to avoid aspiration. The pneumonitis that develops may be treated by the usual measures, oxgen and antibiotics. There are no specific antidotes.

Boric acid and borax (sodium borate) are common household chemicals intended either for use as an eye wash or an antiseptic solution, or to sprinkle around the borders near the door to discourage ants. There are many other uses. They are often put up in packages which are almost indistinguishable from the package of bicarbonate of soda. I have often wondered why we do not see more cases of boric acid poisoning. It seems to be so easy for a person who gets up in the middle of the night to take a dose of bicarbonate of soda to take in its place a teaspoonful of borax. It has no distinctive taste or smell. In spite of this cases of boric acid poisoning in the household are not numerous.

I had one inquiry about a person who swallowed about 4 ounces of a solution containing approximately 6 Gm. of boric acid. He vomited promptly. Such a dose in adults is not apt to cause serious injury and since he seemed to have emptied his stomach fairly well within a few minutes, the doctor was advised to do nothing about it. There was a follow-up in this case and it was established that it had caused no poisoning. I have here the record of another inquiry from a pediatrician. The mother made up the twenty-four-hour formula for her twins and she put 60 Gm. of boric acid into the solution in the place of one of the sugars. The error was discovered at the end of the day when all of it had already been given. It was estimated that about one-half of each feeding had been vomited so that each baby presumably retained 30 Gm. of boric acid. The babies were well forty-eight hours later without any treatment. That is much too long a time without symptoms after a toxic dose of boric acid. The toxicity of boric acid does not seem to be as great as is indicated by the statement found in the literature that 5 Gm. may be fatal to a baby and 15 Gm. to an adult. There must be very marked individual differences in susceptibility. There is here in my folder another story about boric acid. The mother baked a cake and put in a teaspoonful of boric acid instead of baking soda. The baby ate a piece of the cake. Later in the day the mother discovered the error and telephoned to her pediatrician. He found nothing wrong with the baby. He was advised to do nothing about it. Nothing happened to this child but the mother had another question, namely, "Is the cake spoiled"? Apparently it was not as satisfactory a cake as it might have been if it had been made with bicarbonate of soda. I suggested that the cake was edible, but that it would not be wise to permit one member of the family to eat it all. The 5 Gm. of boric acid could do no harm when distributed among the members of the family.

I am, of course, speaking only of household accidents and not of errors of medication. You are undoubtedly aware of the disasters which have occurred in hospitals where boric acid was used in the place of sodium chloride for intravenous infusions. The occurrence of such accidents has created quite a furor in recent years. The question has been debated whether boric acid should not be colored to distinguish it more readily from harmless materials. The whole question of the utility of boric acid has been reviewed. There seems to be considerable doubt concerning its value as a medicinal agent and some hospitals have deleted it from their formularies.

Poisoning by boric acid causes fairly prompt gastrointestinal symptoms, such as vomiting, abdominal cramps, diarrhea, symptoms of circulatory collapse, coma or convulsions, skin eruptions, nephrosis and anuria. There is no specific antidote.

DR. JOHN B. DEITRICK: Would you say how you would treat poisoning by atropine?

DR. GOLD: I know of no specific antidotes to the fatal action of atropine. The only treatment is supportive, and the measures that one might use will depend on the symptoms which seem to be most threatening in the particular case. If the patient presents respiratory depression with cyano-

sis, one might use oxygen. If there is troublesome delirium or convulsions, one might quiet the patient by appropriate doses of barbiturates. Hyperthermia which may result from suppression of sweating can be managed by sponging. There are specific antagonists to atropine, such as prostigmine and mecholyl, but it is doubtful whether any safe doses of these can prevent the fatal action of atropine.

STUDENT: How about the use of pilocarpine?

DR. GOLD: The same applies to pilocarpine. It is extremely doubtful whether any amount of pilocarpine would counteract the fatal action of atropine.

DR. MCKEEN CATTELL: The reverse would be all right, would it not?

DR. GOLD: Yes, atropine is a highly effective antidote against poisoning by the parasympathetic drugs. By means of atropine an animal can be saved from as much as ten times the fatal dose of physostigmine.

Dr. Helpern, you see a great many cases of poisoning in the Medical Examiner's Office. Would you tell us something about these?

DR. MILTON HELPERN: Those in the Medical Examiner's Office are, of course, fatal cases of poisoning. We encounter a large number of them in a year. Unfortunately, our department has no record of the non-fatal cases. There is no agency in the city through which the non-fatal cases are cleared. One would have to comb the hospitals and the records of private physicians in order to secure information on the total incidence of poisoning. A large proportion of the poisonings which we encounter are caused by ordinary household materials.

Illuminating gas is the chief cause of poisoning that we see. The toxic agent in it is carbon monoxide and the latter is responsible for more than one-half of all our cases.

The extermination of household pests provides a rich and varied source of household poisons. I might refer to a few of the more common ones which come to our attention. They are supplied under a wide variety of trade names. There is the roach paste known as the John Opitz roach paste which is widely advertised. It reeks of yellow phosphorus. It is usually placed on pieces of potato or bread under the kitchen sink. Not infrequently the creeping child gets hold of one and munches on it. Since these preparations usually contain from 3 to 5 per cent yellow phosphorus, the child need only consume 1 Gm. or less to be seriously poisoned. He sometimes develops acute gastrointestinal symptoms which direct attention to the poisoning, but the effects may come on more insidiously with signs of acute hepatitis and often the poisoning is not suspected until irreversible symptoms have developed. Poisoning by yellow phosphorus in little children munching on fire crackers on the fourth of July is no longer a serious problem in communities where the use of fireworks has been controlled. There is the more commonly used roach powder which may represent almost pure sodium fluoride. Some protection against poisoning by this material is afforded by the recent law which requires the use of some distinctive dye, such as indigo, to color it blue. You may recall the report some time ago of the group of fatalities in an institution in Oregon where the cook confused the fluoride with flour. I might state that most of the fluoride poisonings which we encounter here are the result of attempts at suicide.

Rat poison is another exterminant which plays an important part in household poisonings. The most common agent is white arsenic. The preparation we have encountered comes in a little, round, wooden box, labeled "Poison." Perhaps the label is responsible for so many cases of suicide with arsenic. I recall one instance of homicidal arsenic poisoning in which a demented sister treated one brother with it on one day and the other the next day. The clinical picture, marked chiefly by gastrointestinal symptoms and collapse, is easily confused with other conditions and in the instance I just mentioned the diagnosis of botulism was made. It is unfortunate that physicians do not include poison-

ing more often among the possibilities when the diagnosis of an unusual disease is considered. I do not know of a case of suicide with arsenic in which the diagnosis was made during life. In the case of the two brothers which was just mentioned it is possible that a prompt and accurate diagnosis on the first boy might have prevented the second poisoning.

An insecticide which sometimes causes poisoning is one containing nicotine. These preparations contain about 40 per cent nicotine sulfate and are used as plant sprays. It causes nausea, vomiting, prostration and sometimes convulsions. It is rapidly fatal in doses of the order of about 50 mg.

Cleansing agents are another fruitful source of household poisonings. There are the strong alkalis, such as lye, concentrated ammonia and washing soda. Every so often baking soda is confused with washing soda and the concentrated sodium carbonate causes serious corrosion. Similar lesions are produced by lye and concentrated ammonia. Strong acids are sometimes found in the home, hydrochloric acid, sulfuric acid and nitric acid. We had a case of a child who drank the soldering fluid his father used when tinkering with electrical equipment. It is a concentrated mixture of zinc chloride and hydrochloric acid and it produced intense corrosion.

Dry cleaning fluids and stain removers are very common household poisons. The more common ones represent carbon tetrachloride, or mixtures of carbon tetrachloride, solvent naphtha, turpentine. benzine, gasoline and kerosene. Cases of poisoning result both from the inhalation of vapors as well as from ingestion. Some time ago we examined the body of a woman who had cleaned a dress with carbon tetrachloride in the bathroom, a small space without ventilation; she succumbed to the fumes of this compound.

Some potent metal cleansers contain cyanide. These solutions find their way into the home without proper labels. The cyanides are commonly used in silver polish. Cyanide is very effective in taking tarnish off silver. It also lends itself to use for suicide. There used to be a preparation known as "Quick as a Wink" and another, "Cinderella" shoe polish, for cleaning metal finished shoes. One of these preparations suggested an antidote on the label, "If taken by mistake, throw cold water on the face." I suppose that was about as useful as any other.

The disinfectants commonly found in the home include such articles as tincture of iodine, carbolic acid, compound cresol solution (lysol) and creosote mixtures. Most of these produce not only systemic poisoning but local corrosive action as well.

I should not omit alcohol, the effects of which are well known. In this connection the solid wood alcohol mixtures such as Sterno and Dry Heat, present a much more serious problem. Alcoholics sometimes resort to these in extremity to prolong an intoxicated state. Rubbing alcohol and other medicated alcohols are also used for this purpose.

Black shoe dye often contains nitrobenzene. It is a potent poison. As little as 1 cc. may prove fatal although 30 cc. have been survived. It is readily absorbed through the skin of an infant's foot as well as by inhalation. It causes bizarre symptoms involving the gastrointestinal tract, the central nervous system and the viscera. Marked methemoglobinemia is an outstanding effect.

DR. GOLD: Dr. Dale is here from the Department of Pediatrics. It would be interesting to learn about the experiences of the pediatrician in this hospital.

DR. JOHN H. DALE, JR.: Our experience is in general agreement with your statement, Dr. Gold. A considerable proportion of the children admitted to this hospital present the problem of poisoning with household drugs, medications and other materials. Most of our patients are between two and three years old. The most frequent poison is fluoride roach powder. As a rule we see the children very soon after they have taken it. Gastric lavage is usually performed in the clinic. The signs and symptoms which

follow are those of gastro-enteritis and so far this has responded satisfactorily to bland diet and fluids. We recently saw a child who bit off the tip of a thermometer and swallowed the mercury. It passed through the intestinal tract in about three days and no signs of poisoning developed. The laxative known as Ex-Lax, which contains phenolphthalein, is another source of trouble for us. The usual story when they are brought in is that they have consumed from twelve to twenty-four of these chocolates. Except for purgation, nothing seems to have happened. One child that took some hydrochloric acid developed burns in the buccal mucosa and gastroenteritis. There was no bloody diarrhea. The recovery was uneventful. Children are commonly brought in with the story of having eaten a box or a book of safety matches. In view of the fact that the phosphorus is on the striking surface we considered it safe to send these children home without treatment. We have seen a few cases of lead poisoning, usually in children with hysteria or pica, who have taken to eating the paint on the stairs, window sills and elsewhere. These have been of the chronic, not of the acute, type of lead poisoning. This about sums up the chief types of cases which we encounter in this neighborhood. There have been no lye burns and no caustic poisonings of any kind.

DR. GOLD: Did most of the children that you have seen recover?

DR. DALE: All of them recovered. We have had no deaths from household poisonings in the past three years.

DR. GOLD: Even all the patients who took fluoride in the form of roach poison?

DR. DALE: Yes. Of course, we do not know how much was taken in these cases. The story is usually obtained from an extremely excited mother, and it is difficult to learn how much was taken but it seems that the children rarely take too much. Our experience bears out your point that overzealous treatment causes more trouble than the poison. As I stated we lavage the stomach with tap water and call it quits. We keep the child under observation for changes in the pulse and for symptoms referable to the central nervous system. We treat gastro-enteritis with a bland diet. That seems to have been enough for our patients.

I might refer to the few cases which we have seen in which the child swallowed furniture polish. In these we have not been able to identify the toxic ingredients. Fortunately all of them recovered. We have seen two cases of acute alcoholism in children less than ten years of age. One of these could hardly be considered an accident since the family fed the child almost a pint of wine. The other was an eighteen month old infant who got his hands on a pitcher of beer and drank quite a bit of it. Both recovered.

When we go back further in the history of this department, we find some cases of poisoning by boric acid, hyoscine, atropine and codeine. Most of these were therapeutic poisonings. We have not had any of these in recent years.

DR. CATTELL: Might you have used calcium in the fluoride cases?

DR. DALE: We did not use it.

DR. GOLD: Are you referring to the value of calcium as a systemic antidote or for its effect in the gastrointestinal tract?

DR. CATTELL: I had in mind the fluoride in the stomach. The sodium fluoride would be converted into the extremely insoluble calcium fluoride if the stomach were washed with soluble calcium chloride.

DR. HELPERN: In your cases, Dr. Dale, was the fluoride recovered and identified by chemical analysis?

DR. DALE: No. We knew the brands of roach powder and the composition was supplied by the manufacturer.

DR. HELPERN: I ask this because fluoride is a very potent poison and it does not take very much of it to kill.

DR. GOLD: One has to take from 5 to 10 Gm. to produce serious poisoning in an adult. Most of the roach powders I think contain somewhere from 30 to 90 per cent sodium fluoride. In the case of the 30 per cent preparations one would need to con-

sume from 15 to 30 Gm. of the powder. That would be quite a meal.

DR. HELPERN: From what I have seen, Dr. Gold, one does not have to eat very much of it to get into trouble. I would recommend only very small doses of roach powder.

DR. GOLD: Dr. Dale, I surmise from what you have said about management of the cases in which a household poison has been taken that it is wise merely to wash out the stomach, observe the patient for a suitable time and then treat special symptoms as they arise, and that you refrain from the use of stimulants and depressants unless there is clear indication for them.

DR. DALE: That is the policy we have followed.

SUMMARY

DR. GOLD: The nature of the problems of household poisonings was explored in this conference. The number of chemicals which may be involved in household accidents is extremely large. No attempt, therefore, was made to exhaust the subject. The comments were confined to some of the more general aspects of the situations and to examples of some of the more common and interesting experiences. While there is fairly abundant information concerning poisons in the numerous texts on general toxicology, industrial toxicology, pharmacology and special articles in the medical literature, these often fail to provide the answers to the specific problems which the physician encounters in the case of a household accident. For example, information on the toxicology of mercury is abundant and readily accessible, but the case of the child who has bitten off the tip of the thermometer and swallowed it presents a special situation; the same is true for the toxicology of nicotine, but it does not quite cover the case of the child who has been munching on cigarettes. In such cases it would help to have at hand such facts as the chance of poisoning or the amount of cigarette tobacco babies are in the habit of eating.

Most accidental household poisoning occurs in infants and young children who go exploring about in the home swallowing chemicals without discretion. There are such items as laxative pills containing strychnine; chocolate cathartics containing phenolphthalein; eye drops containing atropine; hypnotic capsules containing a barbiturate; matches; moth balls containing camphor, naphthalene or paradichlorobenzene; kerosene or gasoline; roach poisons containing phosphorus or fluoride; rat poisons containing arsenic; furniture polish and shoe dyes. These and a few others, such as borax taken accidentally in place of a dose of bicarbonate of soda, or put into a cake by mistake in the place of baking powder, or into the infant's formula in the place of sugar, received attention in the discussion.

Sodium fluoride is a violent poison but the pediatricians pointed out that while one of the common experiences at the New York Hospital is the case of the excited mother with the child who had been trying out roach powder containing sodium fluoride, they have encountered no cases of serious poisoning with this material in recent years although most of them received little or no treatment. There seems to be a wide gap between the accidental taking of a household poison and serious poisoning by it. Apparently the amount taken is usually too small. This is a matter of some importance for so often the real trouble is caused by overzealous treatment.

Unfortunately, many of the preparations containing poisons to which children are exposed in the home fail to provide the physician with a clue to the essential chemical. Opinion was strong in favor of extension of legal requirements for the appearance of the name of the compound on the label to guide the physician in appropriate measures, to allay panic and to prevent unnecessary treatment.

At the end of the session the problems relating to several other agents which participate in household poisonings remained in need of attention, also some of the more specific methods of treatment. These will be considered in a subsequent conference.

Clinico-pathologic Conference

Mediastinal Tumor with Gynecomastia and Superior Vena Caval Obstruction*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, J. S., (B. H. No. 158041), a thirty-four year old, white, married laborer, entered the Barnes Hospital on April 19, 1948, complaining of cough and shortness of breath. The family history was irrelevant. The patient had enjoyed excellent health most of his life, and systemic review revealed that aside from frequent upper respiratory infection he had had no serious illnesses. He had worked as a farmer for a number of years and subsequently was employed as a general laborer in a chemical plant.

Six months before entry to the hospital he was assigned to work in a portion of the chemical factory where he was exposed to sulfur fumes and almost immediately he began coughing. The patient stated that several other men who worked in the same section likewise complained of cough. His cough became almost continuous and was productive of a moderate amount of sputum which was occasionally blood-flecked. After two months he was transferred to the part of the plant in which he had worked originally but his cough persisted. Two months before admission he was examined by his private physician who found evidence of a mass in his chest. About the same time the patient developed dyspnea and orthopnea which progressed rapidly so that he was unable to lie flat without choking; as orthopnea became more severe the patient found it necessary to lean forward in order to breathe at all. He noted that his head began to feel full, that the veins in his neck became prominent and that his right arm became swollen. His cough became so severe that occasionally after a paroxysm the patient lost consciousness for a matter of seconds. He developed persistent fever, his appetite decreased and he complained of abdominal fullness after eating only a very small amount of food. Eventually dysphagia appeared. In the month before admission to the hospital the patient's breasts increased in size; they felt hard but were not tender. His symptoms progressed and he became increasingly weak; following a series of laboratory and roentgenographic studies, which disclosed an increased basal metabolic rate, anemia, leukocytosis and a mass in the chest, the patient was advised to enter the Barnes Hospital. During the course of his illness he had lost 17 pounds.

At the time of entry his temperature was 37.5°C., pulse 94, respirations 28 and blood pressure 110/70 (right arm), 100/60 (left arm). The patient was a well developed but poorly nourished male who appeared acutely ill. He had great difficulty in breathing even though propped up in bed. Violent coughing was almost constant. He was able to breathe somewhat easier when he sat on the edge of the bed and leaned forward. The veins of the forehead, neck and right arm were tightly distended and there was some edema in those areas. The veins of the thorax were likewise dilated. Pallor of the skin and mucous membranes was

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

evident. Enlarged lymph nodes, which varied in size from 1 to 3 cm. in diameter, were felt in the cervical, left supraclavicular, axillary and inguinal regions. In the right infraclavicular region there was a mass 4 cm. in diameter which was thought to be possibly a lymph node. External examination of the eyes was not remarkable; there was no Horner's syndrome. Examination of the fundi revealed extreme fullness of the veins; the nose and throat appeared normal. The neck was swollen but soft, the trachea was in the midline and the thyroid was not palpable. The thorax was symmetrical and expansion was equal. About each breast there was a ring of discoid infiltration, approximately 3 cm. in diameter, which seemed firmly attached to the overlying skin. Examination of the chest revealed flatness to percussion extending 3 cm. to the left and 5 cm. to the right of the mid-sternal line anteriorly. Over this area tubular breathing was heard; similar breath sounds were heard at the right apex posteriorly. There were signs of fluid at the right base but no rales were audible. Except for tachycardia examination of the heart was within normal limits. The abdomen could not be examined adequately because the patient was unable to lie flat, but the liver edge apparently extended about 4 cm. below the right costal margin. The spleen could not be felt. The right testis was described as being atrophic; the left was not remarkable. Rectal examination was negative as was the neurologic examination.

Laboratory data were as follows: Blood count: red cells, 2,790,000; hemoglobin, 8.5 Gm. per cent; white cells, 12,300; differential count: stab forms, 5 per cent; segmented forms, 75 per cent; lymphocytes, 16 per cent; monocytes, 4 per cent. Urinalysis: negative. Stool: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 16 mg. per cent; total protein, 6.3 Gm. per cent; albumin, 3.6 Gm. per cent; globulin, 2.7 Gm. per cent; cephalin-cholesterol flocculation test, 2+; icterus index, 6 units; thymol turbidity, 8 units; prothrombin time, 50 per cent of normal; chlorides, 101 mEq./L., blood indices, within normal limits. Roentgenograms of the chest: films showed the heart to be essentially normal in size and shape. There was a large mass in the superior mediastinum extending further to the right than to the left, and there was evidence of fluid in the right pleural cavity. Small rounded areas of infiltration were scattered throughout both lung fields.

On the night of admission, the patient's respiratory distress became extreme. He obtained moderate relief by use of oxygen and sedation. The following day a biopsy was taken of the left breast. It was reported to show the histologic appearance of gynecomastia with hyperplasia of the ducts and proliferation of fibrous tissue. A presumptive clinical diagnosis of lymphoma was entertained but because of the patient's critical condition it was believed that a therapeutic trial with nitrogen mustard was merited. The patient received daily doses of 6 mg. of nitrogen mustard on four consecutive days; although considerable vomiting and malaise were associated with these treatments, the patient's dyspnea and orthopnea decreased. Coincident with clinical improvement further laboratory studies were undertaken. With the patient at a 45 degree angle, the venous pressure was 350 mm. of sodium chloride. The circulation time (arm to tongue with decholin) was 25 seconds. Following completion of nitrogen mustard therapy, the left supraclavicular node and the right infraclavicular mass decreased in size, but a chest film showed an apparent increase in the size of the mediastinal mass. On the twelfth hospital day the left supraclavicular lymph node was removed; microscopic sections showed almost total destruction of the lymphoid elements by an infiltrating carcinoma. The tumor cells were arranged in broad sheets and exhibited a tendency to gland formation. Abnormal mitoses were frequent and there were numerous nucleated tumor giant cells. The origin of the primary tumor could not be determined from the biopsy specimen.

Because of the gynecomastia, an Asch-

heim-Zondek test was performed and was reported to be positive. Although the patient had shown some symptomatic improvement, roentgen ray therapy was directed to the mediastinal mass with increasing dosage on consecutive days; a total of 3,800 roentgen units were administered. Following blood transfusions, the patient's red cell count rose to approximately 4,000,000. At the conclusion of x-ray therapy there was a slight decrease in the diameter of the retromanubrial mass, but the amount of fluid in the right chest had increased; the parenchymal infiltration of the lungs noted on admission remained unchanged.

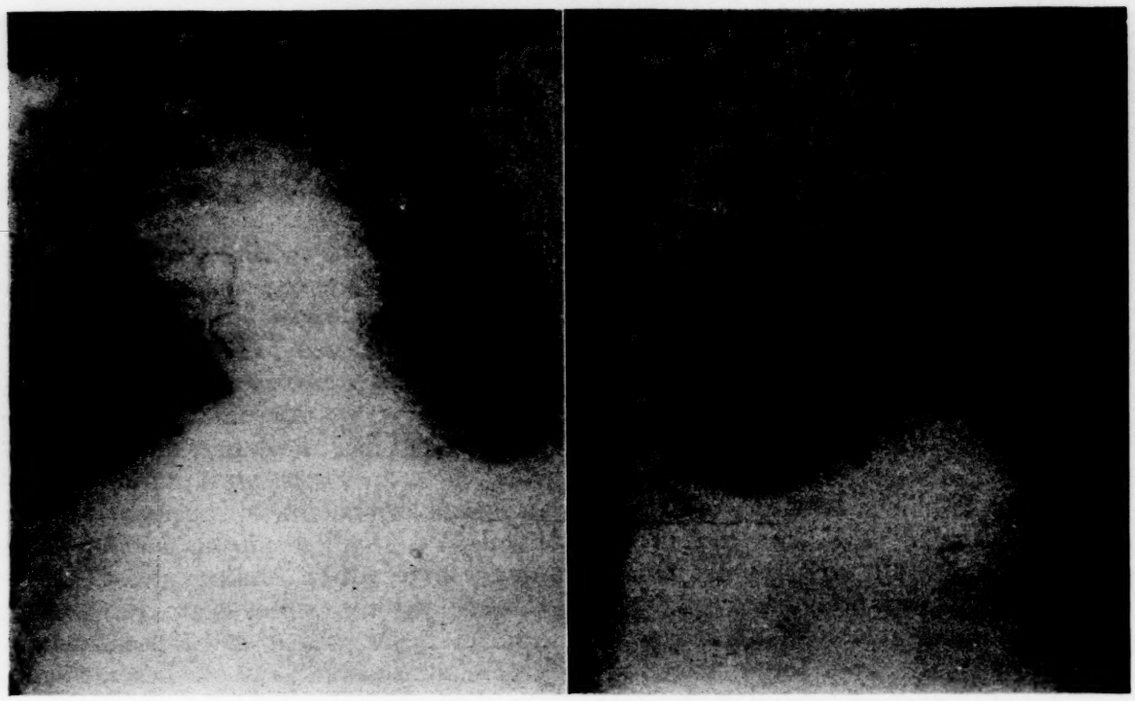
During his last week in the hospital the patient complained of sharp pain in the region of the seventh and eighth ribs in the mid-axillary line, and marked rigidity in the thoracolumbar region of the vertebral column appeared. The testes were reexamined; although it was thought that both were rather atrophic, no tumor nodules could be detected. Shortly before discharge, the patient developed 3+ pitting ankle edema, and his red count fell to 2,800,000. Pain in the left chest persisted, and he required narcotics almost constantly for relief. During his hospital stay his temperature had remained elevated, sometimes being as high as 39°c. At the time of discharge on May 20, 1948, the right infraclavicular mass was noted to be further decreased in size, and the swelling of the neck and face had likewise decreased. The patient was referred to the tumor clinic for follow-up.

After leaving the hospital he continued to have pain in his left chest as he had had during his hospital stay. His cough reappeared and once more paroxysms occurred during which time he lost consciousness. He produced occasional bloody sputum. Dyspnea progressed, abdominal swelling was noted and the patient complained of considerable epigastric discomfort. Gradually his feet again began to swell, the veins in the upper extremities and head again became distended and edema of the lower extremities increased; on June 1, 1948, he was re-admitted for the last time.

Upon admission his temperature was 37°c., pulse 104, respiration 32 and blood pressure 120/80. The patient was markedly emaciated. There was pigmentation of the skin over the regions to which roentgen ray therapy had been directed. The supraclavicular lymph node on the left and the infraclavicular mass on the right were markedly enlarged. Those in the axillary and inguinal regions were enlarged although not to the same degree. Venous engorgement of the face, neck and anterior thorax was marked. There was puffiness of the face, brawny edema of the right arm and hand and marked pitting edema of the lower extremities. Enlargement of the breasts was the same as on the previous admission. Examination of the lungs revealed signs of fluid at both bases, more on the right. Dry rales were heard at the right apex. Retrosternal dullness extended 6 cm. to the left and 6 cm. to the right of the midsternal line. The abdomen was distended, apparently with fluid. The liver edge extended 7 cm. below the right costal margin. As before the testes were small but no nodules could be felt. The remainder of the physical examination was as on the first admission.

Laboratory data were as follows; Blood count: red cells, 3,470,000; hemoglobin, 7.8 Gm. per cent; white cells, 12,640; differential count: eosinophiles, 2 per cent; stab forms, 12 per cent; segmented forms, 75 per cent; lymphocytes, 8 per cent; monocytes, 3 per cent. Blood chemistry: total protein, 5.2 Gm. per cent; albumin, 2.7 Gm. per cent; globulin, 2.5 per cent. The remainder of the blood chemical findings were unchanged from those reported previously. Quantitative Aschheim-Zondek test: negative for 0.5 cc. of serum, positive for 1.0 cc. of serum. Urine ketosteroids: 2.6 mg. for twenty-four hours; sodium pregnandiol glycuronidate; 19 mg. per twenty-four hours.

The patient's course in the hospital was progressively downhill and was charac-



1 2

FIG. 1. Chest film taken shortly after the patient was first admitted to the hospital. In addition to the large mediastinal mass, a number of small nodules are seen throughout the lung fields.
FIG. 2. Lateral view of the chest taken at the same time as Figure 1. Note that the mass lies high in the anterior mediastinum.

terized by increasing cachexia and weakness. At no time was he able to lie down, and for the most part he had to lean forward in order to breathe. He was given large doses of morphine for relief of pain. On one occasion a thoracentesis was performed, and 250 cc. of bloody fluid were removed. The fluid had a specific gravity of 1.020 and contained 2,100 leukocytes and 60 per cent polymorphonuclear forms. Culture of the fluid was sterile.

The patient expired quietly on June 17, 1948.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Dr. Bottom, would you care to discuss the chest films for us?

DR. DONALD S. BOTTOM: The first film (Fig. 1) was taken shortly after the patient's original admission to the hospital and it shows a number of interesting findings. A large mass may be seen in the mediastinum extending well into the right lung field and to a lesser extent to the left. Throughout the lung there are a number of small areas of infiltration, all fairly well circumscribed. Furthermore, in the right pleural cavity a considerable amount of fluid is present. The lateral film (Fig. 2) indicates that the mass lies anteriorly.

The patient was sent to the x-ray department with the clinical diagnosis, "? lymphoma," and the x-ray diagnosis was returned, "? lymphoma." There are some reasons in retrospect which would lead one to question that diagnosis. In the first place the mass lay anteriorly in the mediastinum, and in that area teratomas, tumors of the thymus gland or substernal thyroids are much more common. Lymphoma, which would be more apt to involve the lymph nodes around the hilum, would not in all likelihood be situated as high in the mediastinum. Furthermore, when one reconsiders the small nodules scattered throughout both lungs, he realizes that it would be rather unusual to have that type of infil-

tration in lymphoma; rather, such masses are more typical of metastatic carcinoma. In retrospect, therefore, from a radiologic point of view a diagnosis of metastatic carcinoma would have seemed more suitable than one of lymphoma. Films taken after the completion of the course of x-ray therapy showed the mass to be smaller than it had been originally although the degree of change is not very marked. There was less fluid in the right pleural cavity. The metastatic areas in both lung fields, however, were more prominent than they were originally. A film taken during the second admission (Fig. 3) reveals that the mediastinal mass is considerably smaller than originally, but there is a rather large amount of fluid in both pleural cavities and a still further increase in the size of the metastatic nodules in the lung.

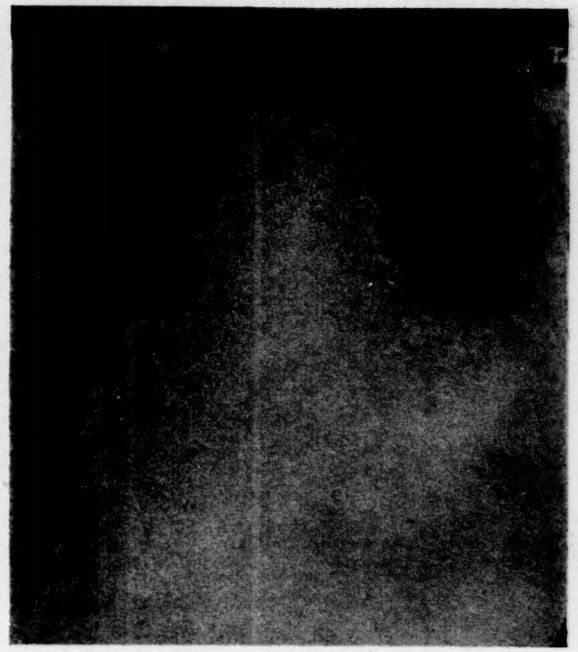


FIG. 3. Chest film taken during the patient's second admission. The mass is somewhat smaller but the amount of fluid in the pleural cavities has increased.

DR. ALEXANDER: This case is most unusual. From the report of the microscopic findings of the lymph node biopsy, it seems likely that this man had carcinoma with metastases which involved the lungs, mediastinum, lymph nodes and possibly the liver. Probably its most unusual feature was the association of gynecomastia, confirmed by biopsy. The origin of the tumor was not apparent to the surgical pathologists, and it is our problem to attempt to identify its primary site. Since gynecomastia does stand out as a striking finding, it would be well for us to review the mechanisms by which it may occur, and I shall ask Dr. MacBryde to comment.

DR. CYRIL M. MACBRYDE: In general, gynecomastia is associated with the presence of abnormally large amounts of estrogenic hormones in the male body. One of the most common causes of gynecomastia at present is the administration of stilbestrol in the treatment of carcinoma of the prostate. Presumably, estrogenic hormone in sufficient amount will produce enlargement of breast tissue in normal males. Unilateral gynecomastia may be seen after injury to one breast; local trauma to the breast can result in gynecomastia possibly because of alteration in the blood supply or because of sensitization of the tissues to amounts of hormones normally present. Gynecomastia is seen occasionally in newborn infants, both male and female; presumably, its occurrence under those circumstances is explained by the estrogen which was transferred to the body of the infant from the mother through the placenta. It usually disappears shortly after birth. Hypertrophy of breast tissue is seen in young boys at the age of puberty but the mechanism is not well understood; it is not a universal finding at that juncture. Gynecomastia occasionally occurs in older men who have a decrease in the production of testicular hormone. In regard to more serious conditions, gynecomastia appears in association with injury to the testes, with tumors of the testes and with certain diseases which result in atrophy of the testes. Cryptorchid testes seem to be particularly susceptible to the development of tumors with which gynecomastia may be associated. It also may be seen with any disease which leads to severe, diffuse liver damage, particularly cirrhosis. The cause usually advanced is that the liver

is unable to inactivate amounts of estrogen normally present in the male.

DR. ALEXANDER: Does gynecomastia occur in association with pituitary or adrenal disorders?

DR. MACBRYDE: Yes, rarely it may.

DR. ALEXANDER: On several examinations this patient was reported to have atrophy of both testes, but no tumor nodules were noted. Dr. Rouse, you saw this patient. Would you describe your findings?

DR. ERNEST T. ROUSE: Both testes were small, but both were definitely present. They were palpated repeatedly for tumor nodules, but none were ever detected. I did not believe that the degree of atrophy was remarkable.

DR. ALEXANDER: Although the patient had a 2+ cephalin-cholesterol flocculation test and an enlarged liver, I do not believe that there was liver damage to the extent necessary to explain gynecomastia on that basis. Dr. Wade, the Aschheim-Zondek test was reported as positive. Under what circumstances may a positive result be recorded other than with pituitary stimulation?

DR. LEO J. WADE: The Aschheim-Zondek test is normally positive during pregnancy and is associated with the appearance of large amounts of chorionic gonadotropic substances. The most common pathologic cause of a positive Aschheim-Zondek test is chorio-epithelioma which may give rise to enough chorionic gonadotropic substance to yield a positive test.

DR. ALEXANDER: Dr. Wood, I understand that you first suggested that this test be performed. Would you tell us your reasons for requesting the procedure?

DR. W. BARRY WOOD, JR.: Members of the house staff and others of us who saw this patient were very impressed by the gynecomastia. We believed as you did that the degree of liver involvement was not sufficient to explain it. Further, the patient had not been starved for a sufficiently long period of time in our opinion. In males one of the causes of gynecomastia is chorio-epithelioma, and for this reason we suggested to the house staff that an Aschheim-Zondek test be obtained in an attempt to confirm that impression. When the positive results were made known, I consulted Dr. Robert A. Moore and told him that the patient had gynecomastia and a mediastinal mass. I asked him whether there could be any possible relation between the two, and he referred me to a paper on teratomas of the mediastinum in which Dr. H. G. Schlumberger, working in the Army Medical Museum, reported the results of a study of all the teratomas in the museum collection.[1] A number of cases of teratoma, instead of originating in the testis, arose primarily in the mediastinum. Having seen that paper, we became very much interested in the possibility that this patient had a primary teratoma of the mediastinum with a chorioepithelioma which had metastized and which had also caused the gynecomastia. That was our working hypothesis while the patient was in the hospital.

DR. ALEXANDER: Is it true that chorioepitheliomas may produce enormous quantities of gonadotropic hormone?

DR. MACBRYDE: Yes.

DR. ALEXANDER: Dr. Moore, are metastases of chorio-epithelioma functional?

DR. ROBERT A. MOORE: In some instances metastases do produce chorionic gonadotropin. That depends in part on the maturity of the tumor. One cannot make a categorical statement, but I believe that it is generally accepted that cytotrophoblasts are the cells which produce chorionic gonadotropin. The cytotrophoblast is characteristic of the early stage of placental development which is the reason why the amount of gonadotropin produced is so high during the first month of pregnancy and then starts to decrease although in relative terms it is still high at the end of pregnancy. Chorio-epithelioma will duplicate the general structure of the placenta in every stage of its development. I can well imagine that at any given stage a metastatic nodule might produce small

[1] SCHLUMBERGER, H. G. Teratoma of anterior mediastinum in group of military age; study of 16 cases and review of theories of genesis. *Arch. Path.*, 41: 398, 1946.

amounts of hormone whereas another might produce huge amounts, depending on the relative number of immature cytotrophoblasts in the particular nodule.

DR. ALFRED GOLDMAN: There are cases reported in the literature in which, following removal of the primary teratoma, chorionic gonadotropin disappeared from the urine only to reappear when metastases from the original tumor became evident.

DR. ALEXANDER: That is a most interesting point, Dr. Goldman. When the Aschheim-Zondek test was done in this case, it was negative with 0.5 cc. of serum but was positive with 1 cc. of serum. Does that finding disturb you?

DR. WOOD: At the time we developed our hypothesis that report was not available; in retrospect, however, although those results are a bit disturbing, they do not make me believe that the diagnosis of chorio-epithelioma need be retracted.

DR. A. LEWIS FARR: It should be noted that the production of chorionic gonadotropin may be quite variable. It is usually stated in textbooks that the amount of gonadotropin produced by chorio-epitheliomas is extremely high. Dr. Willard Allen, however, studied a number of female patients with chorio-epitheliomas in whom production of gonadotropin was not significantly elevated.

DR. ALEXANDER: It is my understanding that the cause of gynecomastia in the male in the presence of excess estrogen. Is there any evidence that chorionic gonadotropin *per se*, gives rise to secondary female sexual characteristics?

DR. MACBRYDE: I do not believe that it alone can produce gynecomastia.

DR. ALEXANDER: Is it not true that gynecomastia is quite rare in males with chorio-epithelioma? I believe that in 1915 when Dr. J. V. Cooke reported the forty-seventh case, his was only the second in which gynecomastia was definitely described; in no other case was mention made of breast changes.[2]

[2] COOKE, J. V. Chorio-epithelioma of the testicle. *Bull. Johns Hopkins Hosp.*, 26: 215, 1915.

DR. MACBRYDE: Certainly all patients with chorio-epithelioma do not have gynecomastia.

DR. WILLIAM H. DAUGHADAY: The endocrine aspects of testicular tumors have been thoroughly reviewed by Twombly.[3] He noted that there may be increased production of progesterone (as indicated by pregnandiol excretion), estrogens and of chorionic gonadotropin as well. Increased estrogen excretion was largely limited to patients with mixed epitheliomas rather than carcinomas. In five of eight such patients the excretion was moderately to markedly increased. There appeared to be a direct correlation between the amount of chorionic gonadotropin and increased estrogen excretion. Gynecomastia was associated with marked increase in urinary estrogen excretion.

DR. ALEXANDER: Dr. Wood, would you concede that the primary site of the tumor could have been in the testis, although it was too small to have been detected clinically?

DR. WOOD: Certainly.

DR. ALEXANDER: In summary, it seems that we agree that this patient had a chorio-epithelioma, probably primary in the mediastinum. Due to the limitation of time, we have been unable to discuss the superior caval syndrome, a classical example of which was seen in this man.

Clinical Diagnoses: Chorio-epithelioma; ?primary in mediastinum with generalized metastases; superior vena caval syndrome due to chorio-epithelioma of the mediastinum.

PATHOLOGIC DISCUSSION

DR. THOMAS L. YOUNG: At autopsy the body showed evidence of considerable weight loss. The skin was pasty gray in color. There was marked pitting edema of the legs and the left thigh and the neck veins were slightly distended. A few nodes

[3] TWOMBLY, G. H. and PACK, G. T. Relationship of hormones to testicular tumors. In Endocrinology of Neoplastic Diseases. P. 228. Oxford University Press. New York, 1947.

were palpable in the left supraclavicular region. Both breasts were enlarged and beneath each nipple freely movable, firm masses, 3 cm. in diameter, were noted. There were also two small subcutaneous nodules just lateral and superior to the areola of the left breast.

There were 1,700 cc. of sanguineous fluid in the left pleural space and 1,100 cc. in the right. The lungs were studded with soft hemorrhagic, umbilicated tumor nodules, varying in size from a few mm. to 3 cm. in diameter. The pleural spaces about both apices were obliterated by dense fibrous adhesions. In the superior mediastinum encroaching on the apex of the right lung, the trachea, the superior vena cava and invading the azygos vein, there was a large mass 8 cm. in diameter; on cut section it was soft and variegated in appearance with many areas of necrosis and hemorrhage. Most of the tumor nodules in the lungs were hemorrhagic although on cut section some were yellowish brown, necrotic and friable.

In the abdomen the tumor surrounded the aorta and obliterated the vena cava and the iliac veins. In the region of the left adrenal there was a large, blue, soft mass which partially replaced the parenchyma of the gland, and numerous smaller tumors were scattered throughout the perirenal tissues. The lymph nodes in the abdominal cavity, including those in the peri-aortic and peripancreatic regions, were invaded by tumor tissue. In addition the tumor had extended retroperitoneally along the aorta, the vena cava and the renal vessels. A few nodules lay near but did not invade the ureters. The liver contained discrete, circumscribed, soft, cheesy, yellowish-white tumor masses varying in size from 0.5 to 4.0 cm. in diameter; only a few were hemorrhagic.

Both testes were atrophic, but in the right testis posteriorly a small firm nodule, 1 cm. in diameter, was palpable. On section the mass was found to be a cyst containing clear, colorless fluid. The left testis and epididymis were normal.

The brain weighed 1,560 Gm. The meninges were congested and a moderate cerebellar pressure cone was present; the unci of the temporal lobes were herniated slightly through the incisura tentorii. The ventricles were slightly dilated and a small mucoid cyst was present in the choroid plexus of the third ventricle. No metastases of the tumor were demonstrable in the brain. The pituitary was grossly normal.

Dr. Robert A. Moore: In this case the primary lesion was a tumor which involved many structures, including the mediastinum, lungs, liver, retroperitoneal lymph nodes and breasts. The tumor was soft and gray-red with numerous foci of hemorrhage; all of the nodules, however, were not converted into hemorrhagic masses such as are usually seen with chorioepithelioma of the testis or mediastinum.

The first section (Fig. 4) illustrates the lobulated architecture of this tumor; a moderately dense connective tissue septum extends across the lower left corner of the field and in it are a moderate number of lymphocytes. Much of the tumor is necrotic as can be seen in the large focus on the right side of the photomicrograph. The tumor itself is not made up of a uniform type of cell; rather, it seems to follow a pattern as it were. In some areas of the section in Figure 4 two cell types may be distinguished; one group consists of large cells with moderately distinct cell borders, vacuolated or reticulated cytoplasm and nuclei which are highly anaplastic in appearance. In some of the nuclei, nucleoli may be seen. The second group of cells shows a good deal of variation. Some of the cells are quite dark with nuclei which are much more chromatic. The architectural pattern is such that the pale large cells are in the center and the smaller more chromatic cells are on the outside. Figure 2 is another view of the tumor in an area of necrosis. It illustrates the association of hemorrhage in close association with these same cells. In Figure 3 the two cell types are seen under higher magnification. At the left of the section a number of pale large cells with

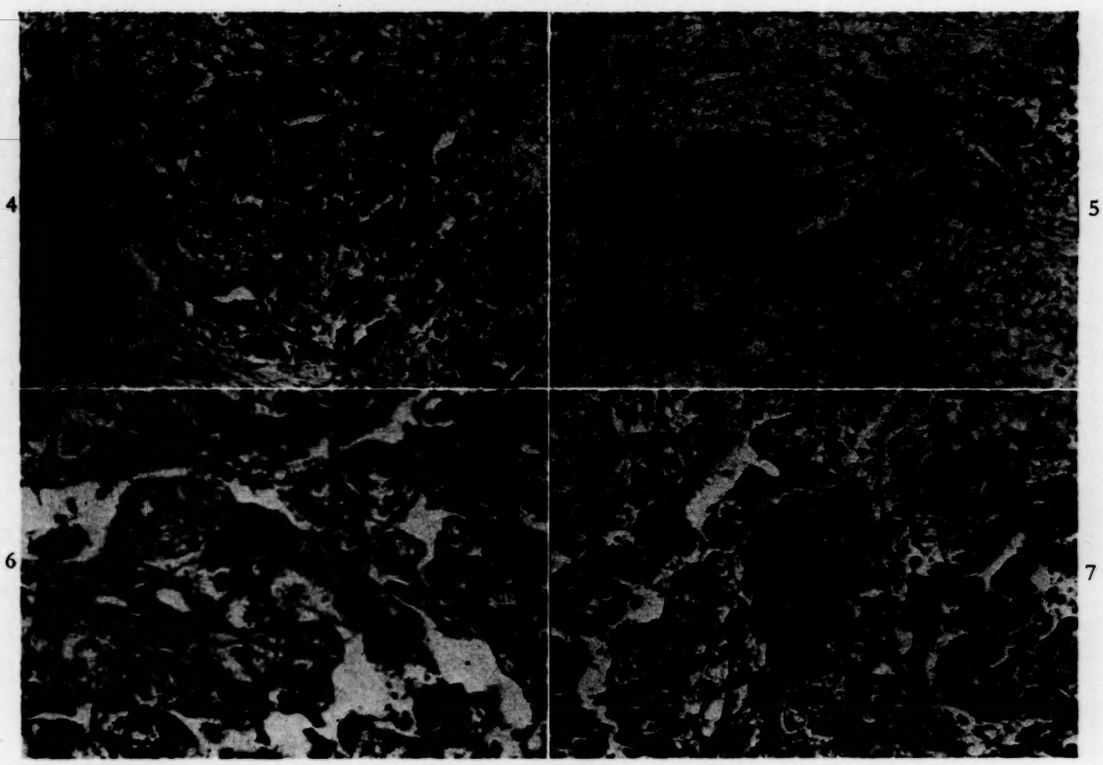


FIG. 4. Metastatic chorio-epithelioma showing the lobulated architecture and a focus of necrosis.
FIG. 5. Hemorrhage and necrosis in close association with the cells of the tumor.
FIG. 6. Cell types within the tumor illustrating the large pale cells with vacuolated nuclei and darker cells with more chromatic nuclei.
FIG. 7. Detailed illustration of the large syncytiotrophoblastic cell and an abortive chorionic villus to the left of center.

vacuolated nuclei are seen; on the right the cells exhibit basophilic cytoplasm and more chromatic nuclei. A detailed view of the large cell type is seen in Figure 4. The cell wall is irregular, there is fine vacuolation and some basophilia of the cytoplasm and the cell is multinucleated. It may be noted that the tumor is characterized by cellular masses in which a large pale cell is surrounded by more chromatic smaller cells.

There can be no question that this tumor is a chorio-epithelioma for it exhibits all of the essential characteristics. There are aborted, very early chorionic villi made up of a cytotrophoblast surrounded by syncytiotrophoblasts. The syncytiotrophoblasts have the typical appearance of those seen in the placenta from the eighth to tenth days of human gestation; it is at this time that these cells produce more chorionic gonadotropin than they do at any other stage of development and maturation. This tumor, which may also be called a choriocarcinoma, duplicates the structure of the placenta. It has a tremendous proclivity for invasion of tissue over and above that which the trophoblastic cell shows in invading blood vessels in the normal placenta.

Let us now consider the fact that in the male chorio-epithelioma may occur primarily in any one of three places: It may arise in a testicular tumor, in the mediastinum or in the region of the pineal body. These three sites may be properly grouped under two headings: gonadal and extragonadal, the tumors arising in the mediastinum and the region of the pineal body being classified together as extragonadal. It is relatively simple to explain the origin of any totipotential tumor cell if it occurs in the gonad but it is more difficult to explain its occur-

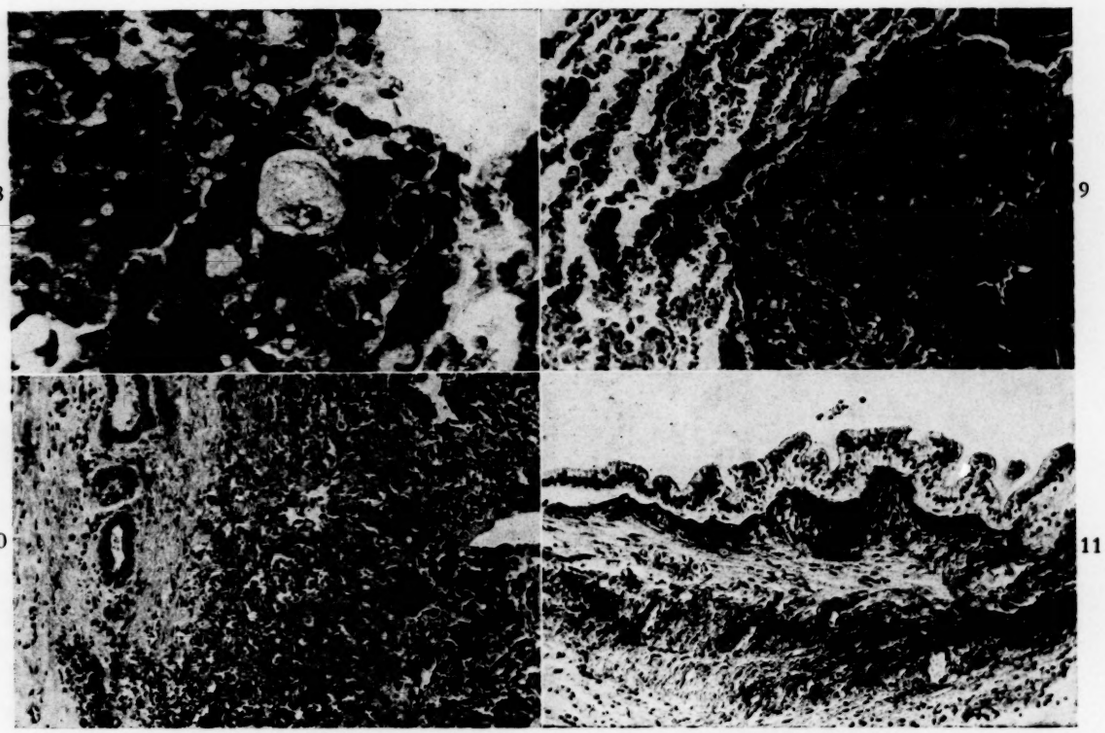


FIG. 8. Metastatic tumor in the liver with the typical architecture of a chorio-epithelioma.
FIG. 9. A section showing metastatic tumor in the lung.
FIG. 10. Section of the breast with changes of gynecomastia on the left and metastatic chorio-epithelioma on the right in a single field.
FIG. 11. Cyst in the wall of the testis. Note that the cells lining the cyst wall are of the tall columnar type characteristic of the alimentary canal. The lamina propria and muscularis are seen underlying the epithelial layer.

rence outside the gonad. It is important to remember, however, that both of the extragonadal sites of origin are in the midline; it seems quite likely that totipotential cells which retain their capacity to produce both trophoblastic and somatic cells are isolated in the blastophore stage of the embryo and come to rest in either of these two sites.

To illustrate further that this tumor was a classical chorio-epithelioma Figure 5 shows a metastatic lesion in the liver; again, there are cytotrophoblasts and syncytiotrophoblasts in typical relation to one another. Figure 6 is a section of the lung in which another metastasis is seen; again, the orientation of the two cell types is typical.

Figure 7 is a section of the breast which confirms the diagnosis of both gynecomastia and metastatic chorio-epithelioma. On the left hyperplasia of the epithelium, thickening of the periductal tissue and slight periductal cellular infiltration are seen; on the right metastatic chorio-epithelioma is apparent.

Dr. Young described a cyst in the testis 1 cm. in diameter and Figure 8 is a section from the wall of the testis showing a cystic space lined with tall columnar epithelium of the type seen in the alimentary canal; beneath the epithelium smooth muscle may be seen.

In view of this finding I believe that a diagnosis of teratoma of the testis must be made and this case assumes great importance in regard to our concepts of the nature of testicular tumors; it represents one of eight or ten in the literature in which there is association of a true adult teratoma of the testis and metastatic chorio-epithelioma although to find a teratoma of the testis that has some other elements in it and

metastatic chorioepithelioma is not unusual. If I propose to you that at some earlier date this patient had a malignant tumor of the testis which metastasized and that subsequently the primary tumor became benign, it will involve some theorizing concerning the nature of testicular tumors. However, I would like to attempt to support just that concept. I think it is becoming increasingly evident that nearly all testicular tumors are of one type although they may show some cellular variations which influence their prognosis. The basic fact in regard to tumors of the testis is that they are derived from a sex cell which probably undergoes parthenogenesis during the course of development of the tumor. Now if indeed such a series of circumstances occur, two cell types may result, namely, trophoblastic and somatic cells. In the normal course of pregnancy the trophoblastic cells become the adult placenta and are discarded at the end of the period of gestation; the somatic cells develop into the organism. A comparable chain of events occurs in testicular tumors. My own hypothesis, which has been accepted and propounded independently by others, is that all testicular tumors go through a phase in which they contain malignant trophoblastic tissue as well as somatic tissue. In some instances the somatic element is lost and eventually only chorio-epithelioma remains. In other instances the trophoblasts are lost and only the somatic portions remain so that an adult teratoma develops. If during the earliest period of development of such a tumor a few trophoblastic cells escape, they may develop into a chorio-epithelioma at a distant site although in the primary site the trophoblasts may disappear and leave only somatic cells to form a benign adult teratoma. I think such a sequence of events occurred in this case. Another possibility which seemed likely when we first examined the testis and found a nodule is even rarer than the one which I have just discussed, namely, that the primary tumor develops from one of the trophoblastic cells, but for some unknown reason it undergoes fibrosis and destruction and ultimately is represented by only a scar. I have seen two such cases in the series that I studied.

I would like to comment briefly on the subject of hormone production by tumors for I think it is most important to correct some of the false impressions concerning the presence of gonadotropin in the urine. In patients with all types of testicular tumors there is an increased amount of gonadotropin, but if an examination is made to distinguish between hypophyseal gonadotropin, originating presumably from the basophilic cells of the pituitary, and chorionic-gonadotropin, originating from cytotrophoblasts, it will be found that hypophyseal gonadotropin is increased in every patient with a testicular tumor. Certain patients with tumors of the testis have in addition large amounts of chorionic gonadotropin and surgical excision of the tumor or its destruction by radiation in no way influences the hypophyseal gonadotropin but merely removes the source of chorionic gonadotropin. The divergence of opinion in the literature concerning the effects of operation on gonadotropin excretion results from the failure to consider the nature of the determination performed; some workers have measured hypophyseal gonadotropin whereas others have determined chorionic gonadotropin. Thus, with more sensitive tests it has been reported that removal of the tumor had no effect on gonadotropin excretion, whereas with relatively insensitive tests which are commonly employed in most laboratories excellent results have been obtained which show that gonadotropin is present before operation but disappears afterward. If this phase of the problem is to be clarified, a sensitive procedure is essential; if that is done, it is found that the only two tumors of practical importance which produce chorionic gonadotropin are the embryonal carcinoma and chorio-epithelioma. Patients with adult teratomas do not excrete increased amounts of hypophyseal gonadotropin as do all patients with testicular tumors.

Finally, concerning gynecomastia, I do

not know that anyone has put forward evidence as to why some patients with chorio-epithelioma have gynecomastia and others do not. I would reason that the estrogen producing gynecomastia comes from the chorionic cell and I think that if one carefully examined the cells of the tumors in those with gynecomastia, one might be able to determine which cellular element or architectural pattern is present only in such patients and absent in those without gynecomastia.

Anatomic Diagnoses: Adult teratoma in the right testis; metastatic chorio-epithelioma in all lobes of the lungs, liver, breasts, subcutaneous tissues of the left thorax, pelvis of the right kidney and the left adrenal gland, and in the iliac, peri-aortic, peripancreatic and anterior and posterior mediastinal lymph nodes; extension of chorio-epithelioma into soft tissues of the mediastinum with invasion of the superior vena cava and azygos vein and the wall of the trachea; chorio-epithelioma involving the retroperitoneal connective tissue about the aorta, inferior vena cava, renal pedicles and ureters; gynecomastia, bilateral.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Editor's Note: Reprints of these conferences are now available. Requests should be sent to Dr. Robert J. Glaser, Department of Medicine, Barnes Hospital, St. Louis 10, Mo.

Case Reports

An Unusual Case of Clonorchiasis with Marked Eosinophilia and Pulmonary Infiltrations*

GEORGE E. CARTWRIGHT, M.D.
Salt Lake City, Utah

A CASE of clonorchiasis with marked eosinophilia in the peripheral blood and bone marrow and bilateral pulmonary infiltrations is presented. The similarity and possible relation of this condition, Löffler's syndrome and tropical eosinophilia (eosinophilic lung) is discussed.

The case presented is of interest for several reasons:

1. Clonorchiasis in army personnel has not been rare. It has been encountered frequently in the China-Burma-India theater. During the winter of 1945 to 1946 a number of patients with leukocytosis, marked eosinophilia and carrying ova of Clonorchis sinensis in the feces were observed in an Army general hospital in Shanghai, China. Heretofore this condition has received very little attention within the United States. The problem will be of importance in returning military personnel, not only from the China theater but also from Korea and Japan. It will now have to be considered in patients presenting marked eosinophilia and the diagnosis, even in experienced hands, is many times difficult. In many cases the ova can be demonstrated only after repeated stool and bile examinations.[1]

2. As far as the author is aware no cases of clonorchiasis with pulmonary infiltrations have been recorded in the literature. This enlarges the growing list of etiologic agents in the production of the so-called Löffler's syndrome.

3. The reported cases of clonorchiasis in which the blood changes have been followed over such an extended period of time are few.

4. The similarity between this condition and tropical eosinophilia (eosinophilic lung) gives rise to several interesting problems.

Clonorchiasis is caused by the presence of the Oriental liver fluke, Clonorchis sinensis, in the biliary passages.[1,3] This fluke occurs in the Far East as a common parasite of fish-eating mammals. The highly endemic regions of human infection are China, French Indo-China, Japan and Korea. The life cycle requires about three months. Man, dogs and cats serve as reservoir hosts. The eggs, laid in the smaller bile passages, are carried down the common bile duct to the duodenum and are passed in the stools. The ova must reach water and are believed to hatch when ingested by appropriate species of snails. Development within the snail requires four to five weeks and includes the production of mother sporocysts followed by a generation of rediae. At the end of this interval cercariae break out of the rediae and emerge from the snail. These cercariae penetrate beneath the scales and into the musculature of fresh water fish where after a developmental period of several weeks they produce cysts. After ingestion of raw or poorly cooked fish by man or other suitable mammalian hosts the cysts are digested and the

* From the Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah.

parasites are released in the duodenum where they become attached to the mucosa. They soon migrate through the papilla of Vater into the common bile duct and then into the smaller biliary radicles, especially those of the left lobe of the liver. Pathologically, clonorchiasis is characterized by proliferation of the biliary epithelium, connective tissue hyperplasia and, in severe prolonged cases with repeated infections, by fatty degeneration, eosinophilic infiltration and cirrhosis of the liver.[4] The majority of infected persons harbor few worms and do not present significant symptoms.[5] A few patients develop edema, diarrhea and hepatomegaly. The most advanced cases are associated with cirrhosis of the liver, anasarca, cachexia and extreme jaundice. No satisfactory treatment has been found. Gentian violet medicinal administered orally is recommended for heavy infections of long-standing. The disease runs a self-limited course in asymptomatic patients with light infections.

CASE REPORT

A white male, aged twenty-one, entered the orthopedic service of a general hospital in Shanghai, China, on April 7, 1946, complaining of intermittent low backache.

Three years previously he had been kicked low in the back by a horse, following which he was in bed for three weeks with low back pain. Since that time, he had had intermittent pain brought on by jolting rides, stooping and weight lifting. On the day prior to admission, following a severe jolting ride in a truck, the pain became severe, especially upon stooping, and he was confined to bed. The pain did not radiate, was localized over the lumbar area and was not accentuated by coughing or sneezing.

The past history revealed that the patient arrived in India in February, 1945. Shortly afterward he developed a mild, productive cough and noticed "bronchial wheezing" especially at night. These symptoms were never severe. On December 22, 1945, he attended a banquet in Kunming, China, and ate poorly cooked native fish. Three months later he developed a bilateral conjunctivitis which lasted two weeks.

The patient gave a history since the age of 13 of numerous attacks of "hives" supposedly due to oranges, tomatoes and strawberries. He had had about twelve attacks of hives in the previous ten months although he had rarely eaten oranges, tomatoes or strawberries. The attacks were relieved by adrenalin and calcium. There was no other history of allergy. He was treated for amebic dysentery in May, 1945. He gave no history of diarrhea since that time.

The family history revealed that the patient's mother frequently developed hives following ingestion of tomatoes. There was no other family history of allergy.

Physical examination disclosed the following: Temperature, 98.8°F., pulse, 82; respiration, 16 and blood pressure, 122/84. The patient did not appear ill. He was somewhat obese with a rather marked lordosis and protuberant abdomen. The conjunctivae were moderately injected bilaterally. The sclerae were not icteric. The color of the mucous membranes was normal. There was slight tenderness on deep palpation over the mid-lumbar spines, the sacrospinalis muscles and both costovertebral angles. There was no glandular enlargement. The liver and spleen were not palpable. The remainder of the physical examination, including examination of the chest, was not remarkable.

Laboratory data revealed the following: Kahn, negative; hemoglobin (Sahli), 16 Gm. per cent; sedimentation rate, 18 mm. per hour; volume of packed red cells, 42 cc. per 100 cc., white cell count, 10,000 per cu. mm. Differential count: metamyelocytes, 2 per cent; neutrophiles, 48 per cent; eosinophiles, 20 per cent; lymphocytes, 26 per cent; monocytes, 4 per cent. Routine examinations of the urine including microscopic examination were unremarkable. A urine culture was sterile. The non-protein nitrogen of the blood was 34 mg. per cent. A Mosenthal concentration-dilution test was normal (1.025 to 1.003 specific gravity). An intravenous pyelogram failed to reveal any abnormalities. X-rays taken of the lumbosacral spines and pelvis were not remarkable. Repeated stool cultures failed to reveal the presence of a pathogenic organism. Twenty-four stool examinations for parasites and ova were negative. No significant abnormalities were noted on proctoscopic examination.

Intracutaneous skin tests were performed with thirteen inhalent allergens, seventeen food allergens, two pollens and two molds, with the

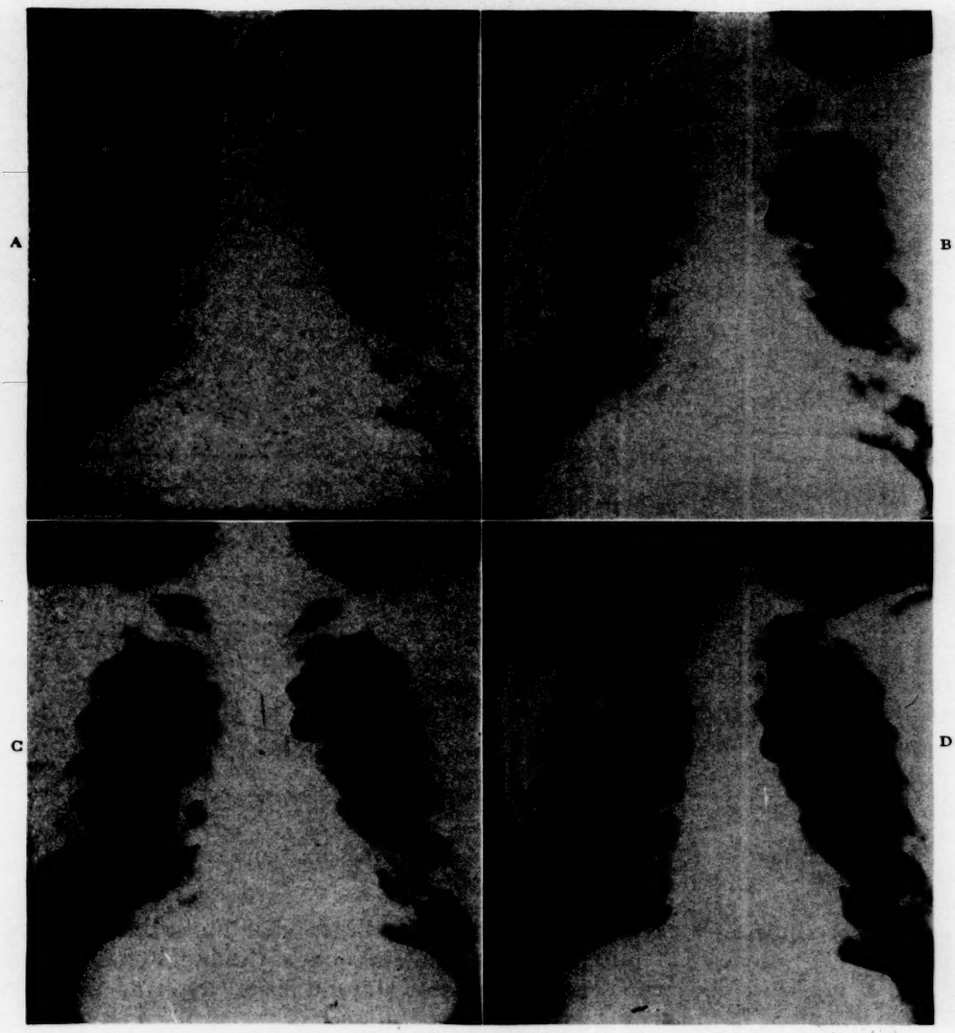


FIG. 1. A, roentgenogram of the chest taken on May 1st showing bilateral lower lung field infiltrations; B, roentgenogram taken on May 6th. There has been noticeable resorption of the process in the left lower lung field; there has been little change on the right; C, roentgenogram taken on May 13th. There has been further resorption on the left but still no significant change on the right; D, roentgenogram taken on June 10th. There has been complete clearing of the infiltrative process in both lung fields. The bronchial markings are somewhat increased.

following positive results: rice, 3 plus; house dust, 3 plus; cow, 2 plus; feathers, 2 plus; yeast, 2 plus; orris, 1 plus; pyrethrum, 1 plus; corn, 1 plus; tomatoes, 1 plus. No sensitivity was found to oranges.

The back pain subsided completely upon heat, rest, acetylsalicylic acid and use of a backboard. On the second hospital day (April 9th) he had a mild shaking chill and the temperature rose to 100.4°F. (oral). A blood smear for malaria was negative. Thereafter the oral temperature fluctuated between 98.0 and 99.2°F. On April 30th the per cent of eosinophiles had risen to 65. The white cell count was 7,600 per cu. mm., the sedimentation rate (Wintrobe hematocrit tube) 17 mm. per hour and the volume of packed red cells 42 cc. per 100 cc. The patient was transferred to the medical service for an investigation of the low grade fever and eosinophilia. On May first examination of the chest revealed dullness to percussion with decreased tactile fremitus and decreased breath sounds over the left lower lung field posteriorly. The roentgenogram (Fig. 1) showed an area of moderately increased density covering the entire left lower lung field below

the eighth rib posteriorly and a small area of moderately increased density located in the sixth right anterior interspace. There were no symptoms, pulmonary or otherwise, at the time. The sedimentation rate was 19 mm. per hour and the cold agglutination titer was not generalized moderate increase in density with an increase in the bronchial markings. The patient developed a mild cough productive of small amounts of yellowish-mucoid sputum. A smear of the sputum stained with Wright's stain revealed that about 50 per cent of the cells

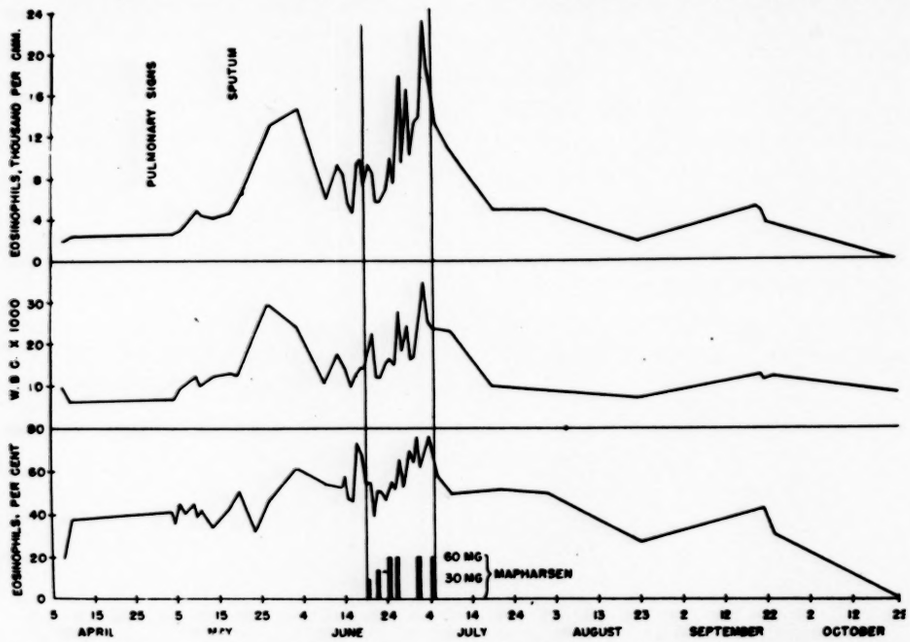


FIG. 2. Showing the effect of mapharsen on the leukocyte count and absolute and relative eosinophilia.

diagnostic. Blood cultures were repeatedly sterile. Typhoid "H" and "O" and paratyphoid A and B agglutinations were not significant. A roentgenogram of the chest taken on May 10th revealed clearing in the left lower lung field but there was no change in the density in the right lower lung field. (Fig. 1B.) By May 13th the left lower lung had cleared still more but the bronchial markings were quite dense. The area of density in the right lower lung was unchanged in size and also seemed to follow the pattern of the bronchioles. (Fig. 1C.) There was no rise in the cold agglutinin titer. Repeated blood cultures were sterile. Between the 8th and 12th of May the temperature fluctuated between 99.0 and 100.0°F. Examination of the chest during this time was not remarkable. There was slight leukocytosis (10 to 13 thousand per cu. mm.) and the eosinophiles fluctuated between 39 and 54 per cent. The eosinophiles were principally normal adult cells with an occasional stab cell. No myelocytes or abnormal cells were seen in the blood smear. On May 20th the lower lung fields bilaterally showed a were eosinophiles. The cough persisted. Physical examination of the lungs again failed to reveal any abnormalities. By May 27th a noticeable resolution had taken place as seen in the roentgenogram. By June 3rd almost complete resorption of the infiltrative process had taken place. The bronchial markings over both lower lung fields remained moderately increased. The cough disappeared and the patient was asymptomatic and afebrile. The white cell count had risen to 24,400 per cu. mm. and the per cent of eosinophiles to 62. The eosinophiles were again adult cells with an occasional band form. No myelocytes or blast cells were seen. Between the 3rd and the 19th of June the white cell count varied between 10,000 and 17,000 per cu. mm. The eosinophiles fluctuated between 45 and 74 per cent. During this period there was complete resolution of the process in both lung fields. The bronchial markings in the right lower lung field were still somewhat increased. (Fig. 1D.) Repeated examinations of fresh specimens of stool were negative for ova and parasites. Aspiration of the sternal marrow on June 7th,

at which time the total white count was 24,200 per cu. mm. and the per cent of eosinophiles was 62, revealed the following information: Myeloblasts, 1.0; promyelocytes, 4.0; eosinophilic myelocytes, 4.0; eosinophilic metamyelocytes, 10.0; eosinophiles, 32.0; neutrophilic metamyelocytes, 5.0; neutrophiles, 15.0; lymphocytes, 16.0; monocytes, 2.0; normoblasts, 9.0; megakaryocytes, 1.0; basophiles, 1.0.

Mapharsen therapy was begun on June 19th. The patient received six intravenous injections (0.31 Gm.) over a sixteen-day period. (Fig. 2.) There was a marked rise in the total white count to 34,900 per cu. mm. and the eosinophiles fluctuated between 40 and 76 per cent. On July 1st ova of Clonorchis sinensis were demonstrated for the first time in the stool. Many ova were seen. This was the twenty-fifth stool examination. Many ova of Clonorchis sinensis were again seen on the following day. By the time the mapharsen therapy had been completed (July 4th) the white cell count and per cent of eosinophiles had begun to fall. During the next three months the white cell count gradually decreased to normal and the eosinophiles diminished to 2 per cent. During this time the patient was afebrile and entirely asymptomatic. Physical examination of the lungs was not remarkable. Stereoscopic films of the chest taken on September 10th were negative. Ova were never again demonstrated in the stool and two examinations of the bile were negative for ova. At no time during the course of the illness was diarrhea present.

Summary. This patient entered the hospital with a complaint of low back pain which was irrelevant to the condition under discussion. On admission an eosinophilia of 20 per cent was present. He was asymptomatic except for the initial complaint. During the hospitalization he developed chills, an intermittent low grade fever and clinical and roentgenologic evidence of bilateral pulmonary infiltrations. The physical signs were fleeting but the infiltrations were slow in resolving. Following detection of the pulmonary lesions, he developed a cough productive of small amounts of sputum containing many eosinophiles, as well as leukocytosis associated with an increase in the eosinophiles in the peripheral blood to 74 per cent. A differential count on the bone marrow obtained following sternal puncture revealed that 46 per cent of the cells were eosinophiles. Following mapharsen therapy, there was an initial increase in the eosinophilia and leukocytosis which was followed by a gradual decline to normal over the course of several months. Diarrhea was not a feature of the illness. The ova of Clonorchis sinensis were demonstrated in two consecutive stool specimens. The patient was not particularly ill at any time; indeed, there was a paucity of clinical symptoms and signs.

The difficulty in the diagnosis of clonorchiasis is well illustrated in this case. The first twenty-four stool examinations were negative. It is difficult to state with certainty when the original infection occurred. To the patient's knowledge the only time he had eaten local fish was on December 22, 1945. Whether the mild pulmonary symptoms which he experienced in India in the early part of 1945 were a part of his illness or a separate one is not known. The symptoms were not severe enough for him to request a medical examination at the time. It is interesting that he had a history of previous allergy and that there was a familial history of allergy to a limited degree. What relation this had, if any, to the patient's symptoms and signs is impossible to state.

COMMENTS

Leukocytosis and eosinophilia have been noted in both experimental[6,7] and human clonorchiasis. A significant eosinophilia and marked leukocytosis are present in most Koreans infected by Clonorchis sinensis.[1] Bercovitz[1] has reported an eosinophilia as great as 48 per cent and a leukocytosis as high as 31,600 per cu. mm. An eosinophilia (10 to 47 per cent) but not leukocytosis has been reported in infected Chinese.[5] In Japan it is stated that clonorchiasis is accompanied by leukocytosis but eosinophilia has been observed in only about 24 per cent of the cases and then it is never marked.[8,9] It would seem that the degree of leukocytosis and eosinophilia varies some-

what according to the race of the host. As further evidence of this during the winter of 1945 to 1946, a number of German patients with fever, jaundice, leukocytosis (10,000 to 30,000), eosinophilia (20 to 80 per cent), pulmonary infiltrations and ova of Clonorchis sinensis in the stools was observed by the writer in a repatriation camp in Shanghai. This, along with the observations made upon American soldiers in China, suggests that in races with little previous exposure the leukocytic and eosinophilic response may be greater.

The clinical syndrome described here fulfills the diagnostic criteria of the syndrome described in 1932 and again in 1936 by Löffler,[10,11] namely, a mild clinical course, transient pulmonary signs, characteristic pneumonic infiltrations roentgenographically, eosinophilia and leukocytosis. Löffler described the roentgenograms as showing homogenous or more often spotty or cloudlike, sharply or less sharply limited, single or multiple, unilateral or bilateral, migratory shadows that appeared and disappeared in three to eight days. Since his original description, cases have been reported in which the pulmonary lesions have persisted longer than eight days. Wright and Gold[12] report that in Löffler's syndrome associated with creeping eruption the pulmonary infiltrations continue over a period of weeks if the cutaneous lesions are not treated. It is now generally agreed that Löffler's syndrome is an allergic phenomenon.[13] The etiologic factors which have been reported are chronic asthma, tuberculosis, coccidioidmycosis, privet shrub pollen in China, pollen of the Convallaria in Europe, Ascaris lumbricoides, Trichuris trichuria, Strongyloides stercoralis, Taenia saginata, Fasciola hepatica, Endamoeba histolytica, Trichinas, cutaneous helminthiasis, brucellas and azosulfamide.[12,13] From the observations reported herein it would seem that Clonorchis sinensis may now possibly be added to the list.

In India during the past six years there has been a growing interest in the recently recognized and commonly occurring condition described as tropical eosinophilia, eosinophilic lung, pseudotuberculosis of the lung with eosinophilia and benign eosinophilic leukemia.[14–19] Clinically, the disorder is variable and the mode of onset is gradual. In the acute stage there is usually fever, a dry hacking cough and symptoms of asthmatic bronchitis. Severe paroxysmal bronchial asthma may develop. Asymptomatic cases have been described. Physical signs when present are those of a mild bronchitis. Splenomegaly and enlargement of the lymph glands may be present but neither are a constant finding. Roentgenograms usually reveal numerous discrete shadows scattered throughout both lungs producing a typical mottled appearance. The sputum when present contains eosinophiles. The most characteristic finding of the syndrome is in the blood. There is a leukocytosis of 20,000 to 80,000 per cu. mm. and the eosinophiles vary from 15 to 90 per cent of the total white cells. Considerable fluctuation of the absolute eosinophile count from day to day has been noted.[19] There is no correlation between the blood findings and the clinical or radiologic pictures. Positive serologic tests for syphilis and high cold agglutination titers have been present frequently.[20,22] The duration of the illness has varied from a few weeks to a few years. The most characteristic feature other than the eosinophilia is the response to organic arsenical therapy. Neoarsphenamine given every fourth day in a course of six (0.15, 0.3, 0.45, 0.45, 0.45, 0.45) injections is highly effective. After the first two or three injections there is usually a rise in the total leukocyte count and in the percentage of eosinophiles. This has been considered by several authors to be diagnostic of the disease.[19,21] The rate of the return of the blood to normal varies but a fall in the leukocyte count and in the percentage of eosinophiles is noted in two to four weeks and usually reaches normal in two to four months. Oral arsenical preparations are equally effective. The disease has now been reported from not only India but also Ceylon, China, America, Havana, Egypt,

Samoa, the East Indies and the Netherlands West Indies.[21] The etiology is in dispute. Mites (acarina) have been repeatedly found in the sputum of patients by some observers and a relation between these and the etiology of the disease has been claimed.[23–25] Others have been unable to confirm this.[19] Strongyloides stercoralis[26] and Microfilaria malayi[27] have been believed to be the etiologic factors in several cases. No particular infestation has been consistently present and in many cases no parasites or ova have been found after repeated blood and stool examinations. Concerning the etiology of this condition, Frimodt-Möller and Barton[14] state "In conclusion, it may be said that much in this clinical entity points to an allergic origin, chiefly because the eosinophilia dominates the syndrome described. But it is possible that there may not be a single agent which causes such a condition, but several."

Eosinophilic lung as described in the literature differs from Löffler's syndrome in several respects. The former disease is usually of longer duration, the symptoms are more marked, the total leukocyte count and the percentage of eosinophiles are usually higher and the pulmonary lesions are more diffuse. Actually these are differences only in degree and it is debatable whether tropical eosinophilia and Löffler's syndrome are actually different diseases. In fact, van der Sar[25] has noted mite infection manifesting itself as tropical eosinophilia in some cases and as Löffler's syndrome in others.

The patient presented here fulfills the diagnostic criteria of both syndromes, further suggesting that there may be no fundamental difference between them. The clinical course and roentgen findings were more characteristic of Löffler's syndrome whereas the extremely high absolute eosinophilia and the response to organic arsenical therapy, with first a rise in the absolute count followed by a fall to normal are, according to Menon,[21] almost diagnostic of tropical eosinophilia. He states "If the total eosinophile count is 5,000/cu. mm. and above, i.e., 25 per cent and more of a total white cell count of 20,000/cu. mm., tropical eosinophilia should be considered first in the diagnosis. If the typical symptomatology is present, the diagnosis is beyond doubt. Even if it is not present, a very high E.S.R. and positive Wassermann and/or Kahn reactions justify such a diagnosis and the consequent therapeutic trial with arsenic. An initial exacerbation with subsequent rapid improvement, clinically after arsenical treatment, will practically settle the diagnosis."

It would now seem desirable to ascertain if all cases of Löffler's syndrome regardless of the etiology respond to organic arsenical therapy in the manner just described. It would also be interesting to determine the effect of such therapy on the course of human as well as experimental clonorchiasis. It cannot be claimed from the extremely limited data presented here that organic arsenicals are effective clonorchicidal agents. The effect may only be hematologic and non-specific or fortuitous.

SUMMARY

A case of clonorchiasis with marked eosinophilia in the peripheral blood and bone marrow and bilateral pulmonary infiltrations is presented. The similarity and possible relation of this condition, Löffler's syndrome and tropical eosinophilia (eosinophilic lung) are discussed. It is predicted that clonorchiasis will be a problem in many of the returning military personnel from China, Japan and Korea and that this condition will have to be considered in patients presenting marked eosinophilia.

REFERENCES

1. Bercovitz, Z. Clinical studies on human infestations with the liver fluke (Clonorchis sinensis). *Am. J. Trop. Med.*, 11: 43, 1931.
2. Faust, E. C. and Khaw, O. K. Studies on Clonorchis sinensis. *Am. J. Hyg.* Monograph series No. 8, 1927.
3. Faust, E. C. Human Helminthology, 2nd ed., p. 222. Philadelphia, 1939. Lea and Febiger.
4. Hoeppli, R. Histological changes in the liver of sixty-six Chinese infected with Clonorchis sinensis. *Chinese M. J.*, 47: 1125, 1933.

5. Otto, J. H. Clinical, pathophysiological and therapeutical aspects of human clonorchiasis. *Far East. Trop. Med., Tr. Ninth Cong.*, 1: 543, 1934.
6. Ito, K. Blood features of the rabbit experimental clonorchiasis. In *Jap. M. World*, 7: 275, 1927.
7. Young, S. The changes in the haematopoietic organs and the blood picture in experimental liver-distomiasis. *Jap. J. Exper. Med.*, 9: 47, 1931.
8. Toidi, G. On the blood feature in a case having infection from Opisthorchis sinensis. *J. Okayama M. Soc.*, 376: 1921. In *Jap. M. World*, 1: 5, 25, 1921.
9. Toyama, G. Ueber den Blutbefund bei Leberdistomiasis. *Okayama Igakkai-Zasshi*, 384, 1921. In *Jap. J. M. Sc.*, 1: 59, 1922.
10. Löffler, W. Zur Differential-diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie). *Beitr. z. Klin. d. Tuberk.*, 79: 368, 1932.
11. Löffler, W. Die flüchtigen Lungeninfiltrate mit Eosinophilie. *Schweiz. med. Wchnschr.*, 66: 1069, 1936.
12. Wright, D. O. and Gold, E. M. Löffler's syndrome associated with creeping eruption (cutaneous helminthiasis). *Arch. Int. Med.*, 78: 303, 1946.
13. Herbut, P. A. and Kinsey, F. R. Transitory pulmonary infiltrations (Loeffler's syndrome) in rabbits. *Arch. Path.*, 41: 489, 1946.
14. Frimodt-Möller, C. and Barton, R. M. A pseudotuberculous condition associated with eosinophilia. *Indian M. Gaz.*, 75: 607, 1940.
15. Weingarten, R. J. Tropical eosinophilia. *Lancet*, 1: 103, 1943.
16 Simeons, A. T. W. Pseudo-tuberculosis of lungs with eosinophilia. *Indian M. Gaz.*, 78: 271, 1943.
17. Treu, R. Pseudo-tuberculosis of the lungs with eosinophilia. *Indian M. Gaz.*, 78: 70, 1943.
18. Hodes, P. J. and Wood, F. C. Eosinophilic lung (tropical eosinophilia). *Am. J. M. Sc.*, 210: 288, 1945.
19. Jhatakia, K. U. Observations on eosinophilic lung. *Indian M. Gaz.*, 81: 179, 1946.
20. D'Abrera, V. St. E. and Stork, K. G. Serological reactions in tropical eosinophilia. *Indian M. Gaz.*, 81: 282, 1946.
21. Menon, C. K. Tropical eosinophilia: some further observations. *Indian M. Gaz.*, 81: 70, 1946.
22. Viswanathan, R. Pulmonary eosinophilosis, *Indian M. Gaz.*, 80: 392, 1945.
23. Carter, H. F. and D'Abrera, V. St. E. Mites (acarina). A probable factor in the aetiology of spasmodic bronchitis and asthma associated with high eosinophilia, *Tr. Roy. Soc. Trop. Med. & Hyg.*, 39: 373, 1946.
24. D'Abrera, V. St. E. Further observations on cases of asthma and bronchitis associated with high eosinophilia and with mites in the sputum. *Indian M. Gaz.*, 81: 414, 1946.
25. van der Sar, A. Pulmonary acariasis, its relationship to the eosinophil lung and Löffler's syndrome. *Am. Rev. Tuberc.*, 53: 440, 1946.
26. De Langen, C. D. Anguillosis en het ziektebeeld van de idiopathische hyperosinophilie. *Geneesk. tijdschr. v. Nederl.-Indië*, 67: 973, 1928.
27. Meyers, F. M. and Kouwenaar, W. Over hypereosinophilie en over een merkwaardige vorm van filariasis. *Geneesk. tijdschr. v. Nederl.-Indië*, 79: 853, 1939.

Co-existent Chronic Glanders and Multiple Cystic Osseous Tuberculosis Treated with Streptomycin*

C. Ray Womack, M.D. *and* E. Buist Wells, M.D.

Nashville, Tennessee *Boston Massachusetts*

The co-existence of glanders and osseous tuberculosis is a rare occurrence. This is a report of a recently observed case in which both infections were present. The unusual character of the case and the treatment with streptomycin† warrant this report.

Glanders in man is an uncommon occupational disease of protean nature. Preventive measures have almost eradicated the disease in the equine species and consequently in man.[7]

In 1906 Robins[9] analyzed 156 cases of human glanders collected from the literature. Stewart[10] in 1904, Gaiger[3] in 1913, Bernstein and Carling[1] in 1909, Burgess[2] in 1936, Mendelson[8] in 1936, Herold and Erikson[4] in 1938 and Howe and Miller[5] in 1947 contributed to our knowledge of the human disease.

Human infection with the causative micro-organism, Malleomyces mallei, presents a varied clinical picture characterized by the formation of granulomatous lesions in the skin and subcutaneous tissues, chronic ulceration of mucous membranes with profuse discharges from the nose, mouth and throat, or pulmonic and pleuritic manifestations. Any one or all of these sites may be involved and the picture may be complicated by metastatic hematogenous spread to meninges, bones, joints and abdominal viscera. The disease may run an acute, fulminating, fatal course or it may persist chronically with remissions and exacerbations for as long as fifteen years. A few patients recover spontaneously; the majority die. The clinical picture is greatly complicated by the concurrence of osseous tuberculosis as was present in one of the cases cited by Robins.[9]

CASE REPORT

A. E. R., a blacksmith, age fifty-four, was admitted to the Vanderbilt University Hospital, December 10, 1945, complaining of cutaneous abscesses. For about a year before the present illness he had repeatedly shod mules suffering from chronically draining ulcers of the legs and had frequently contacted pus from these lesions. The present illness began six years before admission when he developed a small ulcer on the left forearm accompanied by slight malaise and fever. A month later tender, generalized adenopathy developed. A cervical node was excised and examined. The histologic report was "acute and chronic inflammatory tissue." The surgical wound rapidly broke down and at the site an indolent ulcer developed which drained purulent material for a period of three to four months; eventually it healed. However, intermittently during the subsequent years tender nodules involving the skin of the neck, chest and extremities developed. These would spontaneously rupture and drain thick, yellow pus and were accompanied often by fever and occasionally by shaking chills. During the intervening periods he apparently felt well.

A year before admission he noted swelling, redness and tenderness of the scrotum which persisted until his admission to the hospital. Four months later pain and deafness developed

* From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

† The streptomycin used was furnished by Dr. Chester S. Keefer, Boston, Mass.

in the right ear in association with a foul, purulent discharge. Both drainage and deafness persisted. Two weeks before admission paralysis of the right side of the face occurred.

The past history was not remarkable. Nasal "catarrh" had been present since childhood and nasal secretions were somewhat more profuse during the present illness. During the six years prior to admission he gradually lost 30 pounds in weight.

Upon admission to the hospital the temperature was 98.6°F., pulse rate 70, respiratory rate 20, and blood pressure 125/85. He was well developed but very poorly nourished and appeared chronically ill. There were depressed, stellate scars about the neck, upper chest, hands and legs. On the left forearm near the wrist were two swollen, encrusted lesions with surrounding erythema. From these thick, creamy pus could be expressed. There was generalized, soft swelling about the left wrist. The right wrist and metacarpophalangeal joints were ankylosed. A firm, slightly fluctuant nodule was present on the dorsum of the right hand. The lymph nodes were generally enlarged and firm but were not tender. A peripheral type of right facial paralysis was present. There was a thin, foul, purulent discharge in the right auditory canal and the drum was perforated, thick and white. He was almost deaf in this ear; the Weber test showed no reference of sound, and Rinné's test revealed bone conduction to be greater than air conduction on the right. The nasal mucosa was raw and inflamed and there was a slight mucopurulent discharge. The chest was symmetrical and thin. A harsh friction rub was heard at the base of the right lung posteriorly and signs of a small, right-sided pleural effusion were present. The heart appeared to be normal. The liver was palpable two fingerbreadths below the right costal margin; it was smooth and not tender. The spleen was not felt. The scrotum was enlarged to about twice the normal size and was tender, red, brawny and thickened. The scrotal wall did not pit upon pressure. It transmitted light and appeared to contain fluid. The reflexes were not remarkable.

Laboratory data included a red blood count of 4,000,000 with a hemoglobin value of 11.0 Gm. The white blood count was 7,450 with a normal differential count. The sedimentation rate was 34 mm. per hour (Wintrobe). The Kahn test and the Wassermann reaction of the blood were negative. Urine and stool examinations were normal. The blood non-protein nitrogen level and phenolsulfonphthalein excretion were within normal limits. The total serum protein was 6.4 Gm. per cent (2.9 Gm. albumin and 3.5 Gm. globulin; A/G ratio, 0.8). The blood calcium, phosphorus, alkaline phosphatase and acid phosphatase values were normal. A Congo red test gave normal results. The bromsulfalein and cephalin-cholesterol flocculation tests of liver function were normal. The cerebrospinal fluid was sterile and normal in all other respects. Repeated blood cultures yielded no growth.

An x-ray of the chest revealed thickened apical pleura bilaterally and both right interlobar fissures were visible. A small pleural effusion was present on the right. The heart was not enlarged. X-rays of the skeleton showed widespread bone atrophy and several destructive lesions. There was an area of bone destruction 3 cm. in diameter in the region of the right mastoid. Areas of bone destruction of variable size and shape were present bilaterally in the radiuses, ulnas, metacarpals, phalanges, taluses and in the medial malleoli of the tibias. A lesion measuring 5 by 1 cm. in the distal end of the left femur showed elevation of the overlying periosteum and some changes suggestive of bone production.

Attempted aspirations of the swollen left wrist and of the nodular lesion on the dorsum of the right hand were unsuccessful. A right thoracentesis yielded 40 cc. of amber fluid which clotted upon standing. It contained 1,500 red cells and 560 leukocytes per cu. mm.; 68 per cent of the latter were polymorphonuclear cells. The specific gravity of the fluid was 1.025, and the protein content 6.25 Gm. per cent. Gram-stained smears of this fluid showed no organisms and cultures produced no growth. No acid-fast organisms were demonstrated by smear or guinea pig inoculation.

Stained smears of pus from the right ear and the ulcer on the left wrist revealed gram-positive cocci in clumps and chains and numerous, small, slender, lightly stained gram-negative bacilli which were preponderantly extracellular. They presented the typical appearance of M. mallei. Curved and slightly clubbed forms were numerous and they presented a beaded appearance. The microscopic picture was strikingly similar in morphology and grouping to tubercle bacilli but they were not acid-fast.

Cultures of the pus on blood agar yielded

many colonies which were readily identified as Staphylococcus aureus and beta hemolytic streptococci. Among them, and in marked excess at twenty-four hours, were numerous, small, "dew-drop," translucent colonies. These were composed of organisms identical morphologically and in their staining reaction with the gram-negative bacilli observed in direct smears. Isolated in pure culture, this micro-organism showed the typical growth behavior of M. mallei except that attempts to grow the organism on potato to demonstrate the typical colony growth and pigment production were unsuccessful. These bacteria were insensitive to penicillin *in vitro* but growth was completely inhibited by 3 micrograms of streptomycin per cc. of culture medium.

Agglutination reactions performed with the patient's serum and the bacilli were positive in dilution up to 1:1,280. The patient's serum agglutinated a known strain of M. mallei, obtained from the American Type Culture Collection, in dilutions up to 1:256.

Although the above data were suggestive that the organism was a strain of the glanders bacillus, conclusive evidence was not obtained until cross-agglutination studies were performed. Antisera were prepared by immunizing rabbits with the patient's organism and with the known type strain of M. mallei. Serum immune to the patient's organism agglutinated the homologous strain in dilutions up to 1:640 and M. mallei up to 1:160. Serum immune to the type-strain agglutinated the homologous organism in dilutions up to 1:160 and the type-strain in dilutions up to 1:640.

It is of interest that specimens of the patient's serum were sent to the Bureau of Animal Industry, U. S. Department of Agriculture, and to the Army Veterinary School, Washington, D. C., for complement fixation tests against M. mallei. The results were negative in each instance.

Diagnostic intradermal tests with commercial mallein were performed during his several admissions after the above serologic studies were obtained. The amount employed in testing ranged from 0.1 cc. of 1:100,000 dilution on the first admission to 0.1 cc. of the undiluted antigen. In this instance a zone of tender, red swelling 3 by 5 cm. in diameter appeared within three hours. It was unaccompanied by any constitutional reaction and disappeared within twenty-four hours. This result was interpreted as being non-specific.

Guinea pigs inoculated intraperitoneally with the entire forty-eight-hour growth of the bacillus on a blood agar slant did not succumb to infection as expected, nor could the micro-organism be recovered by culture from the peritoneum seventy-two hours after injection. This was presumed to be due to the organism's low virulence. Guinea pigs inoculated subcutaneously with pus obtained directly from the ear and skin ulcers did not show evidence of acute infection nor did the so-called Strauss reaction develop.

Acid-fast bacilli were not demonstrated in smears of pus from the ear or from the draining cutaneous ulcers. However, injection of this material into guinea pigs, as mentioned above, resulted in the development of tuberculosis. Acid-fast bacilli typical of Mycobacterium tuberculosis were readily demonstrated in smears from the lesions produced. Fluid aspirated from the bone cyst in the right radius was sterile on routine culture but induced tuberculosis when injected into guinea pigs. Pus aspirated from a subcutaneous abscess which appeared on the dorsum of the right hand shortly before the patient's second admission contained acid-fast organisms which proved to be tubercle bacilli upon guinea pig inoculation. An intradermal test with 0.1 mg. of old tuberculin produced a positive reaction in forty-eight hours.

Repeated sputum examinations were negative for tubercle bacilli. During subsequent admissions and during the follow-up studies material from the ear and the draining lesions was examined repeatedly for tubercle bacilli but none were demonstrated.

Penicillin, 20,000 units intramuscularly every three hours, was administered for ten days. Within about four days the right facial paralysis had entirely disappeared and there was great improvement in the cutaneous lesions. The erythema surrounding the lesions subsided considerably and there was great reduction in the purulent drainage. Cultures from the ear and left wrist after completion of the course of penicillin yielded neither staphylococci nor streptococci. A pure culture of M. mallei was obtained.

Upon completion of the course of penicillin treatment streptomycin hydrochloride, 0.2 Gm. intramuscularly five times daily, was started. Within twenty-four hours severe swelling and pain developed in the left wrist, accompanied

by aching in the knees, ankles and elbows. On the fourth day of streptomycin treatment the temperature rose to 100.2°F. The patient experienced severe arthralgia and pain on movement of all the joints. The right mastoid region became tender. The fever, arthralgia and mastoid pain subsided the following day and he remained afebrile thereafter. The inguinal and femoral lymph nodes decreased in size. Six days after the initiation of streptomycin treatment the glanders bacillus could not be cultured from the ear or skin lesions. The patient was discharged on his thirty-third hospital day having received a total of 13.0 Gm. of streptomycin. All skin lesions were encrusted, had ceased draining and appeared to be healing. The ear continued to drain but drainage was greatly decreased.

He was readmitted on February 12, 1946, for re-evaluation. During the interval he had felt well and had gained 16 pounds in weight. The right ear had continued to drain following his discharge from the hospital but no cutaneous abscesses had developed until four days before admission when one appeared on the dorsum of the right hand. Pus aspirated from the lesion contained M. tuberculosis. A sinus tract later formed at this site and discharged sporadically. During this admission it was impossible to culture the glanders bacillus from any site which previously had yielded it nor could it be demonstrated on direct smear. X-ray examinations of the chest and the bones revealed no significant changes. He was discharged after ten days.

During the following nine days pain and redness involving the right ankle and generalized arthralgia developed accompanied by malaise and chilly sensations. A right inguinal node had become swollen and drained spontaneously and intermittently. He was readmitted to the hospital on March 2nd for a second course of streptomycin. Attempts to demonstrate the glanders bacillus in material from the ear, the draining sinuses and the healing cutaneous ulcers again failed; neither could tubercle bacilli be found. Streptomycin hydrochloride in the previous dosage was again administered, with total dosage of 10.0 Gm. A transient exacerbation of the arthritis and arthralgia again occurred although the reaction was milder than the previous one and was unaccompanied by fever. The course in the hospital was entirely afebrile and uneventful and he was discharged after thirteen days.

Follow-up studies were obtained at approximately two-month intervals for a period of six months. During this time he improved but was unable to assume full activity. He remained afebrile and gained weight slowly. The ulcerated area on the left wrist, the sinus tract on the dorsum of the right hand, the right ear and the inguinal sinus drained occasionally. Neither organism previously isolated could be demonstrated in these discharges. Roentgenograms of the involved bones showed no remarkable change except for the right mastoid in which there was some evidence of healing.

In December, 1946, the patient was seen at another hospital complaining of right-sided pleuritic pain, dyspnea, fever and occasional chills. Two thoracenteses were performed on the right yielding a total of 1,500 cc. of amber fluid which was sterile on culture. Examinations for tubercle bacilli, including cultures, were negative. The patient left the hospital improved and was readmitted in March, 1947, in a critical condition, very dyspneic and emaciated. Thoracentesis yielded only 500 cc. of amber fluid. A chest x-ray contributed no significant information. One day after admission the patient suddenly complained of excruciating chest pain and rapidly expired. Permission for necropsy was not obtained. Clinically, it was believed that death was due to coronary occlusion or possibly pulmonary embolism. During both admissions it was the opinion of his physician that no significant change had developed in the condition of the sites showing intermittent drainage.

COMMENT

There seems to be little doubt that this patient had both chronic glanders and tuberculosis of bone, the latter corresponding to the osteitis tuberculosa multiplex cystica of Jüngling.[6] The tubercle bacillus was recovered from the bone cysts, subcutaneous abscesses and material from draining sinuses overlying the bone lesions. Gram-negative bacilli morphologically resembling the glanders bacillus were isolated from the right ear and from an ulcer on the left wrist, sites which overlay destructive osseous lesions. Cross agglutinations indicated these organisms to be identical with a type culture of M. mallei.

The glanders bacillus was found to be insensitive to penicillin *in vitro* but was moderately sensitive to streptomycin. Penicillin caused partial healing of the skin lesions, apparently by eliminating pyogenic cocci, but had no effect on the glanders bacilli. Streptomycin effected further striking improvement in the skin ulcers and draining sinuses. Following streptomycin therapy M. mallei could not be demonstrated in the lesions again. There was no significant change in the x-ray appearance of the bone lesions. It seems probable that streptomycin cured the patient of glanders but had little effect upon the tuberculosis, unless the tendency toward healing of the sinus tracts overlying bone lesions might be considered such an effect. It should be emphasized that due to a limited supply the dosage of streptomycin was small and whether or not larger doses would have had a more favorable effect upon the tuberculosis cannot be stated. The efficacy of sulfadiazine was not determined in this patient. Howe and Miller[5] found this drug effective both in experimental animal infections with M. mallei and in their six acute cases.

The patient's transient reaction of fever, arthralgia and exacerbation of pain in the lesions, which occurred at the onset of both courses of streptomycin, was of great interest. Early lots of streptomycin occasionally caused reactions consisting of fever, arthralgia and headache, supposedly due to histamine-like substances in the less completely purified drug. Such reactions have been most infrequent recently. The fact that a similar reaction occurred in this patient on two occasions, with different lots of streptomycin, and that it was an exacerbation of pre-existing symptoms seem to indicate a reaction to bacterial protein similar to the Herxheimer reaction seen in syphilis under treatment.

The mallein test and the complement fixation test for glanders were repeatedly negative. These results do not invalidate the diagnosis of glanders. A number of Robins'[9] cases had negative mallein tests. Two of the six cases reported by Howe and Miller[5] had negative complement fixation tests and one had a negative mallein test.

The patient's scrotal inflammation was interesting and the similarity to the Strauss reaction in guinea pigs was striking. No attempts were made to demonstrate the presence of the glanders bacillus in this area.

SUMMARY

1. A case is presented in which chronic glanders and cystic tuberculosis of bone coexisted. The causative organisms of both diseases were isolated and identified.*

2. Penicillin therapy was ineffective. Treatment with streptomycin seemed to be curative for glanders but in the dosage used had little or no effect upon the tuberculosis of bone.

REFERENCES

1. Bernstein, J. M. and Carling, E. R. Observations on human glanders. *Brit. M. J.*, 1: 319–325, 1909.
2. Burgess, J. F. Chronic glanders. *Canad. M. A. J.*, 34: 258–262, 1936.
3. Gaiger, S. H. Glanders in man. *J. Comp. Path. & Therap.*, 26: 223–236, 1913.
4. Herold, A. A. and Erikson, C. Human glanders: case report. *South. M. J.*, 31: 1022, 1938.
5. Howe, C. and Miller, W. R. Human glanders: a report of six cases. *Ann. Int. Med.*, 26: 93–115, 1947.
6. Jüngling, O. Ostitistuberculosa multiplex cystica (eine eigenartige Form der Knochentuberkulose). *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 27: 375–383, 1919–1921.
7. McGilvray, C. D. The transmission of glanders from horse to man. *Canad. J. Pub. Health*, 35: 268–275, 1944.
8. Mendelson, R. W. Glanders. *Ann. Int. Med.*, 10: 43–48, 1936.
9. Robins, G. D. A study of chronic glanders in man with report of a case. *Stud. Roy. Victoria Hosp., Montreal*, 2: 1, 1906.
10. Stewart, J. C. Pyemic glanders in the human subject. *Ann. Surg.*, 40: 109–113, 1904.

* We are indebted to Dr. Roy C. Avery and Dr. G. John Buddingh of the Department of Pathology and Bacteriology, Vanderbilt University School of Medicine, for their assistance in isolating and identifying the micro-organisms from this case.

Hemochromatosis*

Cardiac Failure Associated with Extensive Hemosiderosis of the Myocardium

HOWARD L. HORNS, M.D.

Minneapolis, Minnesota

ALTHOUGH the occurrence of extensive hemosiderosis of the myocardium in cases of hemochromatosis is a frequent autopsy finding, associated disturbances of cardiac function have rarely been noted. For this reason the present case is of interest.

CASE REPORT

The patient, a fifty-four year old male, entered the University of Minnesota Hospital on the otolaryngology service February 10, 1945, with complaints of bilateral hearing loss and left-sided facial paralysis of eight months' duration. He had had chronic otitis media since the age of two following scarlet fever, and in June, 1944 he had suffered acute bilateral ear infections followed by complete hearing loss. Two weeks later complete left facial paralysis suddenly appeared. In July of the same year an increase in thirst, appetite and urine output was noted and at the same time a brownish pigmentation of the hands, arms and groins was observed for the first time. The diabetes was controlled with 35 to 40 units of protamine insulin daily.

Three years before admission the patient had a series of attacks of transient, severe precordial pain radiating into the neck. The attacks were not related to exertion and were untreated; after a few weeks they ceased and did not recur. However, during the succeeding months he noted mild exertional dyspnea and orthopnea requiring two pillows for comfortable slumber. For one month prior to admission slight ankle edema which disappeared with rest was present. The past history was otherwise non-contributory. By occupation he had been a farmer and day laborer. His alcohol consumption was limited to an occasional glass of beer. There were no other instances of diabetes or of excessive pigmentation in members of his family. He was married and had two children.

Upon physical examination the patient was found to be a well developed, middle-aged male in no acute distress. The skin was diffusely pigmented with a grayish brown color marked on the face, hands, forearms, linea alba, intercrural regions and scrotum.

Except for ectropion of the left lower lid the eyes were normal. There was paralysis of both upper and lower facial muscles on the left side and the tympanic membranes of both ears were completely destroyed. No other abnormalities of the head and neck were noted.

The chest was of normal contour and the lung fields were clear. The heart was slightly enlarged, a soft systolic murmur was audible over the entire precordium but was not transmitted to the axilla. The pulse rate was 80 with a regular rhythm; blood pressure ranged from 106/60 to 120/70 on a series of determinations.

The liver was found to extend 9 cm. below the costal margin in the right mid-clavicular line and the spleen was palpable 3 cm. below the costal margin. Both were described as being smooth, firm and non-tender. Except for the scar of an old hernial repair the remainder of the abdomen was normal.

There was slight, but definite pitting edema of the feet and ankles; the reflexes were physiologic.

Laboratory examination revealed the following representative findings: Urine: specific gravity, 1.010–1.031; pH, 5–7; glucose, 0–4; erythrocytes and leukocytes consistently absent; occasional casts. Blood: hemoglobin, 13–14.4 Gm.; red cells, 5,040,000; leukocytes, 4800–7450, with a normal differential count. Blood chemistries: blood urea nitrogen, 11 mg. per cent; blood sugar, 67–327 mg. per cent; CO_2

* From the Department of Internal Medicine, University of Minnesota Medical School and University Hospital, Minneapolis, Minn.

combining power, 69 volumes per cent; blood chlorides, 596 mg. per cent; blood cholesterol, 148–189 mg. per cent. Total plasma proteins were 6.2 Gm. per cent, with 3.6 Gm. of albumin and 2.6 Gm. of globulin. Of the liver function studies the total serum bilirubin was 1.2 mg. per cent with 0.4 mg. per cent in the 1-minute prompt reacting fraction; the cephalin cholesterol test showed 2+ and 3+ flocculation at twenty-four and forty-eight hours; there was 80 per cent of normal excretion of hippuric acid and the serum alkaline phosphatase value was 16 Bodansky units. There was 10 per cent retention of phenolsulfonphthalein dye and the urine urobilinogen was consistently elevated to 12 to 15 mg. daily. The arm to lung circulation time was 12 seconds and that for arm to tongue 19 seconds; a venous pressure of 7 cm. of citrate solution was recorded in the antecubital vein.

Chest x-ray was interpreted as showing a slightly enlarged heart of the left ventriculae type. Electrocardiogram revealed borderlinr QRS voltage, isoelectric T_1 and questionably diphasic T_2.

During the course in the hospital a radical endaural mastoidectomy was done on the left side in the hope of relieving the facial paralysis. This was of no avail and lid suture was carried out to prevent injury of the left cornea. The clinical diagnosis of hemochromatosis was confirmed by liver biopsy. The diabetes was controlled without difficulty and the ankle edema disappeared with rest. He was discharged on March 17th.

During the succeeding two months the diabetes was controlled without difficulty. However, the patient was incapacitated by progressively increasing edema of the lower extremities, with the ultimate development of scrotal edema and ascites which necessitated re-admission to the hospital on May 14th. At this time the physical findings differed from those of the previous admission in the presence of massive edema of the legs and scrotum, shifting dullness in the flanks and scattered rales in the lung bases posteriorly.

The laboratory findings were essentially the same as before. The total serum protein was 6.5 Gm. per cent with 3.7 Gm. of albumin. The venous pressure was markedly elevated, being 18.5 cm. of citrate; arm to tongue and arm to lung circulation times were 13 and 29 seconds, respectively. The electrocardiogram at this time showed much lower QRS voltage in all leads and diphasic T_1 and T_2.

The patient was treated with digitalis, low salt diet and mercurial diuretics; however, his edema progressively increased while at bed rest; dyspnea, orthopnea and mild cyanosis appeared. Terminally he developed convulsions which were not related to hypoglycemia; he then became comatose and expired on June 12th.

At autopsy the body was that of a well developed male with pigmentation and marked edema as previously noted. The abdomen was protuberant with ascitic fluid. The pleural cavities each contained 600 cc. of clear yellow fluid. The right lung weighed 540 Gm., the left 460 Gm.; bronchi and pulmonary vessels appeared normal. The heart weighed 440 Gm., the ventricular walls were hypertrophied and there was some dilatation of the left ventricle. The valves were entirely normal. The muscle was quite brown and flabby; on cut section there was no evidence of infarction or fibrosis. The coronary arteries showed no evidence of arteriosclerosis; they were soft and easily distensible throughout. The liver weighed 1,940 Gm. and was finally nodular and pigmented. The spleen weighed 800 Gm. and was firm and dark red in color on section. The pancreas was deeply pigmented; the adrenals appeared normal. The right and left kidneys weighed 200 and 220 Gm., respectively; no abnormalities were noted. The aorta was normal.

Microscopically, the lungs contained many heart failure cells and exhibited some areas of atelectasis. The muscle fibers of the heart were pale-staining. There was fragmentation in some areas, with an increase in the spaces between the fibers. Cross striations were only faintly present or were absent. The muscle fibers were heavily infiltrated with pigment which stained blue with ferrocyanide. In some areas the muscle substance appeared to be almost entirely replaced. The other organs showed the ordinary findings of hemochromatosis.

COMMENTS

Hemosiderin deposition of severe degree within the muscle fibers of the myocardium is a common autopsy finding in cases of hemochromatosis. Sheldon[1] in his extensive review reported such deposits present in 90 per cent of the cases which included ade-

quate microscopic data to permit evaluation. Althausen and Kerr[2] noted this finding in thirty-three of forty cases they reviewed. Despite this frequency of demonstrable involvement, cardiac symptoms have not been a conspicuous feature in the clinical picture of hemochromatosis. Sheldon[1] notes that there have been some instances of heart failure and in classifying his cases as to cause of death he groups 10 per cent under "various intercurrent conditions and myocardial failure." He fails to state whether any of the ordinary causes of heart failure were present in these cases. However, he apparently did not consider the cases remarkable so presumably the heart failure was considered due to the ordinary causes.

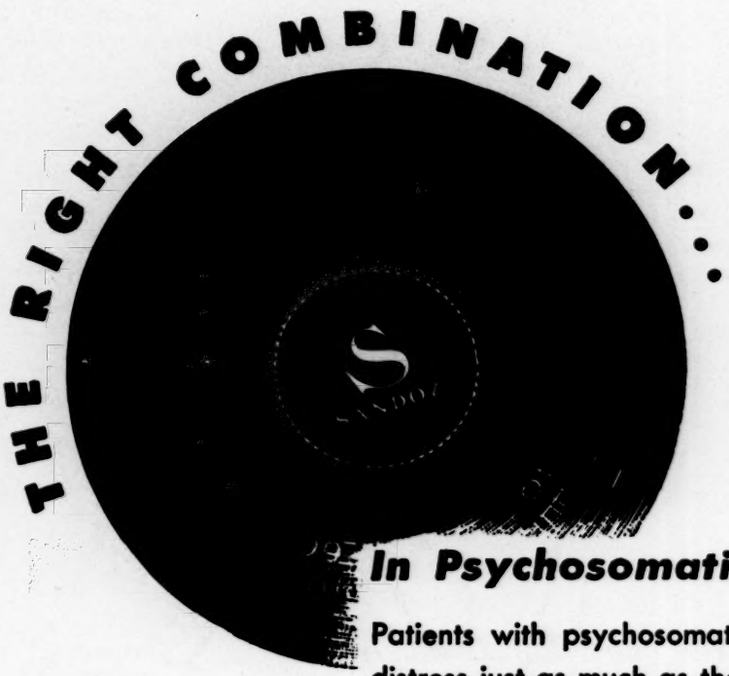
In French literature[3,4] heart failure is noted to be a regular occurrence in what is perhaps a special group of cases of hemochromatosis. A symptom complex is described under the name of the endocrino-hepatocardiac syndrome which is characterized by the following features: occurrence in a younger age group; multiple involvement of the endocrine glands, particularly the testes which are atrophic; infantilism and death from cardiac decompensation. Because myocardial infiltration could not be demonstrated in the autopsy material of some of these cases, most of these authors thought that the heart failure was not explained on a basis of myocardial damage by hemosiderin deposits but rather was due to a generalized metabolic disorder of uncertain nature.

Recent English and American literature contains reports[5–8] describing a total of nine cases of hemochromatosis in which cardiac symptoms have been prominent. Of these subjects six died and autopsies have been performed. In all of them extensive hemosiderin deposits were present in the myocardium; one,[6] however, had coronary disease in addition. In the others the coronary arteries were normal, no valvular lesions were present and there were no histories of hypertension. It is of interest that in three of these cases severe precordial pain with radiation was such a prominent symptom that in two a diagnosis of coronary occlusion was made and later disproved at autopsy. The most common electrocardiographic change has been low voltage. There was complete heart block in two and auricular fibrillation in two others.

In the present case it is believed that with the exclusion of valvular lesions, coronary disease and hypertension as causes of heart failure the cardiac symptoms must be attributed to myocardial degeneration associated with extensive hemosiderin deposits within the heart muscle.

REFERENCES

1. Sheldon, J. H. Haematochromatosis. London, 1935. Oxford University Press.
2. Kerr, W. J. and Althausen, T. L. Hemochromatosis. Report of three cases with endocrine disturbances and notes on previously reported case. Discussion of etiology. *Endocrinology*, 17: 621, 1933.
3. Bezancon, F., deGennes, L., Delarue, J. and Oumansky, V. Cirrhose pigmentaire avec infantilisme, insuffisance cardiaque et aplasies endocriniennes multiples. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 48: 967, 1932.
4. deGennes, L. and Germain, A. Sur deux nouveaus cas de cirrhose pigmentaire avec infantilisme et défaillance cardiaque (syndrome endocrino-hepatocardiaque), *Bull. et. mém. Soc. méd. d. hôp. de Paris*, 56: 665, 1940.
5. Petit, Donald W. Hemochromatosis with complete heart block. *Am. Heart J.*, 29: 253, 1945.
6. Blumer, G. and Nesbit, R. R. Case of hemochromatosis with degeneration of heart muscle and death from congestive heart failure. *New England J. Med.*, 218: 295, 1938.
7. Murray, Lyon, R. M. Haemochromatosis: report on 3 cases. *Brit. M. J.*, 1: 1297, 1936.
8. Maling, T. C. and Riley, G. Haemochromatosis: report on case. *New Zealand M. J.*, 36: 314, 1937.



In Psychosomatic Medicine

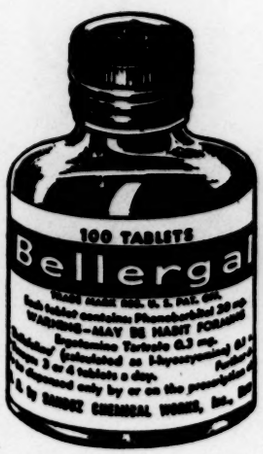
Patients with psychosomatic disorders suffer somatic distress just as much as those with organic disease.

The need for an effective combination of drugs having action on both divisions of the autonomic nervous system as well as the central nervous system is realized in **Bellergal.**

For best results in the treatment of anxiety, and of gastric, cardiovascular and gynecological neuroses, use **Bellergal** as an aid to psychotherapy.

ONLY BELLERGAL PROVIDES:

1. **Sympathetic inhibition with *ergotamine tartrate.***
2. **Parasympathetic inhibition with *Bellafoline.***
3. **Central sedation with *phenobarbital.***



Bellergal S SANDOZ

Originality • Elegance • Perfection

SANDOZ PHARMACEUTICALS
***Division of* SANDOZ CHEMICAL WORKS, INC.**
68-72 CHARLTON STREET, NEW YORK 14, N. Y.

Your acne patient

cooperates

when you prescribe Acnomel...

Because: ACNOMEL is delicately flesh-tinted. It effectively masks the blemishes and blotches of acne—yet is virtually invisible after application.

ACNOMEL ordinarily brings definite improvement —not in months or weeks, but in a matter of days.

Thus, the use of ACNOMEL changes the acne patient's typically defeatist attitude toward treatment. Encouraged, he will faithfully follow the regimen you prescribe and apply ACNOMEL regularly, as you direct.

Available, on prescription only, in specially-lined 1½ oz. tubes.

Smith, Kline & French Laboratories, Philadelphia

Acnomel

a significant advance, clinical and cosmetic,

in acne therapy

uterine

the potent synthetic estrogen...

RECENTLY, Rakoff and co-workers* have observed that the incidence of uterine bleeding is significantly low when menopausal syndromes and related entities are treated with White's Dienestrol—a new, highly effective estrogen. In addition Dienestrol was found to be unusually well tolerated; clinical side effects are almost nonexistent.

Available: DIENESTROL TABLETS: 0.1 mg. (white) and 0.5 mg. (red) in bottles of 100 and 1,000.

AQUEOUS SUSPENSION OF DIENESTROL: In 10 cc. rubber-stoppered vials, 5 mg. of Dienestrol per each cc.

White's

DIENESTROL

- Improvement commences in 3-5 weeks
- Diminished frequency of bowel movements
- Increased stool consistency
- Disappearance of gross blood and mucus
- Sigmoidoscopic evidence of mucosal healing follows symptomatic improvement

CRYMONASE

a specially processed whole defatted duodenal substance

Clinically Effective in NON-SPECIFIC ULCERATIVE COLITIS

Clinical investigations, based on the hypothesis that non-specific ulcerative colitis is the result of a deficiency of an intrinsic factor normally present in the intestinal mucosa, showed effective response following the oral administration of defatted, desiccated duodenal mucosa.

CRYMONASE is a new specially processed duodenal substance whose chief action is the reduction of secretions of the gastro-intestinal tract and a decrease in motility. Special processing prevents autolysis of the substances normal to the raw tissues and they are retained in their natural state.

Supplied—Tablets: Bottles of 100, 250, 500, 1000; Powder: 4-oz. bottle by weight. Literature on request.

Gill, A. M.: Proc. Roy. Soc. Med. 39:517, 1946.

IRWIN, NEISLER & CO. DECATUR, ILLINOIS